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MORAL PROBLEMS IN THE PRACTICE OF MEDICINE*

With Analogies Drawn from the Profession of the Ministry

WILLARD L. SPERRY, M.A., D.D., S.T.D., AND LITT.D.†

CAMBRIDGE, MASSACHUSETTS

MAY I begin what I have to say to you this afternoon by thanking Dr. Means for his kind invitation to me to share your staff meeting with you. And may I add my thanks to all of you for your co-operation in the Institute of Pastoral Care, which heads up at the Massachusetts General Hospital.

The fact that I am here at all and that this institute is centered at your hospital is symptomatic of one of the most significant facts in our life today — the fact that, as in the natural sciences, so in the sciences of man and in the professions, the party walls between fields of specialization are not so high as they once were. When I began my ministry I kept bachelor's hall with a well known surgeon. Occasionally I went his rounds with him. One night he routed me out to go along with him to a hospital. He was giving oxygen to a dying patient. As we came out of the room he said, "She'll be gone before morning." I asked, "What happens to her then?" He replied, "That is your business, not mine. You and I are never in the sick room at the same time. We meet at the doorway. You come in as I go out." That would hardly be said today. Our professions may not coincide, but they do overlap.

May I continue by saying that the standards of your profession are, on the whole, higher than those of any of the other professions. I say this without disparagement of the earnestness and the devotion of the members of my own profession. But the separation of church and state in America forbids the state to do anything whatsoever to maintain decent minimal standards for the ministry, whereas the Commonwealth can and does require of you an adequate education before you may practice medicine. Not only so, but your own professional ethics, over and above the competence required by law, maintain your usage at a very high level. Take a single instance. A professional man is not supposed to advertise. If the newspapers carried, day by day, medical parallels to the advertisements run by the churches on a Saturday and the publicity that ministers allow themselves on Monday, any doctor who sanctioned such self-advertisement would find himself charged at once with unprofessional conduct. I do not hesitate, in dealing with students in the Divinity School, to call attention to the high ethical standards that prevail in the field of medicine.

I have been asked by Dr. Means to talk about certain problems that we share together — problems that are more properly moral rather than medical. We shall come to cases a little later on. But I have to warn you, as I warned him in accepting his invitation, that these problems have no single, simple solution. However, Havelock Ellis once said that the important thing is not to find a man who knows the answer to your problem, but to find a man who knows what the problem is. Were I minded to do so I could cite problems in the practice of my own profession that are, in principle, substantially those which Dr. Means had in mind in inviting me here. I merely ask you to take it for granted that I am not wholly unfamiliar with the type of situation that you face.

When we talk about morals and ethics we may mean one of two things. The two words mean, linguistically, the same thing — the *mores* or the *ethos* of a society; that is, the mean high-water mark of accepted manners in a given society. Thus a recent *Handbook of Psychiatry* (Overholser and Richmond) says, "Conscience is not something that is born in the individual, but something that is acquired from the practices, the beliefs, the attitudes and the customs of the group with which the individual identifies himself. For the average individual his conscience is the crystallized attitude of his group." This is a purely naturalistic, sociologic account of morals. It makes large room for relativity in the whole field of ethics, and for the changes in moral standards of which all of us are aware.

On the other hand there are persons, and these in the main professedly religious persons, who are not content to define and dismiss morality as a

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†Dean, Harvard Divinity School.

matter of social custom. Such persons feel that the distinction between right and wrong, in whatever terms these two words may be defined, has about it a certain absolute quality. Thomas Carlyle says that the greatest moment in modern European history was that when a lonely man stood before a hostile court and said, "It is dangerous to sin against conscience." Most of us have had moments in which we were aware of that danger. In the ancient Wisdom Literature of Israel there is a verse in which God says, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To "forsake oneself" is a serious business; the process may eventually become suicidal for character.

Therefore, I commend to you another account of morals by Father George Tyrrell:

> The rock of irresistible reality is conscience — the sense of right and its absolute claims. No analysis, no explaining away can permanently destroy this faith or lay the ghost. Only conscience can say, "Thou shalt have no other gods before me; thou shalt not bow down to them or worship them, for I the Lord thy God am a jealous God."

The sciences of man can prove beyond all contradiction the relativity of moral judgments at any given place and time. A practice that yesterday was declared to be permissible, if not right, is today declared to be forbidden and wrong. Polygamy and human slavery are two historic instances of this proposition. The prodigal varieties of moral judgment, and the fact, which each one of us has verified in his own experience, that conscience is educable, inclines the sociologist to regard the whole matter as one of ethical relativity. But the religious man cannot abandon altogether his conviction that, whatever its particular pronouncement at any given moment, the principle of conscience has an absolute warrant. No rationalization can explain, much less explain away, this conviction, which has its origins in the belief that the life of man is lived in touch with an "Infinite Mystery" and that our attempts to distinguish between right and wrong have their ultimate origins in the nature of "The Eternal Goodness." The process of ethical culture still goes on, but the quality of an ethical conviction remains constant.

To come more closely to our immediate subject: the actual moral choices that we have to make in this world are seldom between black and white; they are between shades of gray. One of my friends, who taught the undergraduate classes in ethics at Yale, used to say that once we have chosen the lighter shade of gray, we must then, for all practical purposes, go ahead on the assumption that it becomes for us a clear white.

The narrator in Conrad's *Lord Jim* says of his tragic hero that, given his dilemma, there was only a hairbreadth, only the thickness of a sheet of paper, between right and wrong. Once again all of us have had experience of this narrow margin between our moral options.

The most serious and by far the most difficult moral decisions we have to make are those that involve two rival loyalties, each of which is wholly good on its own premises, but which cannot be easily squared. I cited you a moment ago Father George Tyrrell. There is in his autobiography a poignant passage that harks back to just such a collision of loyalties in his own early life. He had felt a call to the religious life and had decided to join a religious order. But his decision meant abandoning to their own fate a needy mother and sister who, humanly speaking, had simple prior claims upon him. Looking back on his decision he said years later:

> Well I remember my last day at home, my last day with those two now hid in death's dateless night, who were my share of the world, the best this life has had for me — whom I forsook for what? in the name of all that is sane and reasonable? For a craze, an idea, a fanaticism? Or for the love of and zeal for the truth, the Kingdom of God, the good of mankind. Had I been faithful to my duty all along, had I stayed at home and supported my mother and sister and made their sad narrow lives a little wider and brighter, would not God have given me light needful for my salvation? Have I done so much good to others who had no claim on me to atone for my neglect of those who had every claim? What have I given up or forsaken for the service of God, as I suppose some would call it, except my plain duty? These are the pleasant doubts that fill my mind in the spare moments, and make me say, Surely I have lived in vain.

In his *Oxford Lectures on Poetry*, A. C. Bradley has an essay on "Hegel's Theory of Tragedy." He points out that tragedy is never a matter of a conflict between good and evil. Such a conflict is forthright and never tragic. The essence of tragedy is, as we have said, a matter of a collision of two loyalties, each of which is wholly good on its own ground:

> The essentially tragic fact is the self-division and intestinal warfare of the ethical substance, not so much the war of good with evil as the war of good with good.... The family claims what the state refuses, love requires what honor forbids. The competing forces are both in themselves rightful, and so far the claim of each is equally justified, but the right of each is pushed into a wrong because it ignores the right of the other.

Professor Bradley illustrates this thesis at great length from the great Greek tragedies and from those of Shakespeare. Clytemnestra has killed her husband and her king. Orestes, her son, is ordered by Apollo to avenge his father, but to kill one's mother is itself a sin against filial piety. The bond of father and son demands that which the bond of son and mother forbids. Richard Lovelace, on going to the wars, says to his *Lucasta*:

> Yet this inconstancy is such
> As you shall too adore;
> I could not love thee, dear, so much,
> Loved I not honour more.

This was Othello's tragedy: his passionate love of Desdemona and his duty to his honor were at the final fatal moment incompatible, so he "put out the light."

The essence of tragedy, then, is not pain or suffering. The essence of tragedy is waste. We are confronted again and again with what William James has called "a forced, momentous option." This option cannot be avoided; a choice must be made, but when it is made something good in itself is inevitably lost.

In this analysis of our moral problems we come here to an area of life where crude rules of thumb, which serve the humdrum needs of every day, are of little help. We must go to art, and perhaps to religion, to understand the nature of our dilemma and to find there some element of resignation and reconciliation.

To come to still closer grips with our problem let me take two or three instances of the tragic dilemma with which we are only too familiar. At these points the professions of medicine and the ministry constantly overlap. Please understand that what I may say hereafter provides no dogmatic resolution of the tragic dilemma. I offer merely my own reflections upon situations that are even more familiar to you than they are to me, and yet situations that, over the years, I have shared with you. For there are times when a patient asks a priest or minister or rabbi questions that he shrinks from asking his doctor.

Telling the Patient the Truth

This issue was, you remember, one that was vigorously debated here in these very circles some years ago, when a gallantly and remorselessly sincere man urged truth telling at all costs.

One might dodge the issue by asking in turn, with Pilate of old, "What is truth?" Bacon said that Pilate was merely a jester, who would not stay for an answer. My observation is that many wise physicians and surgeons are cautious about claiming finality for their diagnoses and prognoses. In the order of nature there are run-of-the-mill diseases that, humanly speaking, must apparently go their normal course to the end. It is a matter of common knowledge that the faith-healing sects in this country have made much of their capital out of hasty and erroneous diagnoses. Some would-be truth teller, who misinterpreted the facts, has dismissed them, perhaps to the ministry of devout believers, but certainly to the *vis medicatrix naturae*. This, however, is more immediately your problem than mine. Furthermore, as one of you said to me not long ago, we never know when some new treatment and possible cure may come suddenly around a corner. Years ago a little daughter of Dean Inge of St. Paul's and a son of L. P. Jacks were taken to London hospitals in the last stages of diabetes, to await the first insulin that was being flown to England from Canada. The girl, alas, died; the lad lived to get his insulin and still lives happily.

But when there is reasonable assurance as to diagnosis and prognosis, what are the doctor, and the minister who shares the doctor's opinion, to do?

Much, perhaps all, depends on a patient's temperament and mental state at the time. Resolute natures, in full possession of their wits, usually want to know what we think and expect, and are able to "take it." I see no reason or warrant for withholding what we believe to be the truth from such a person. I mentioned that Yale professor a few moments ago. He had an obscure illness and died untimely, after going the rounds of specialists in both New York and Boston. He was a man of quick intellect and good courage. He once said to me, in a mood of discouragement and temporary bitterness, "I no longer believe anything that any doctor says to me. They have all lied to me so consistently that I have lost all faith in them." This was a bit of deliberate overstatement on his part, but I think he meant that he was tired of being cheered up by a too facile optimism, or dismissed with deliberate perplexity.

On the other hand many persons do not even ask themselves how ill they are, let alone asking any one else. They prefer to take what comes, as it comes. The reticence of such persons should be respected. There is no occasion and no moral obligation to intrude the supposed truth upon such minds. To do so would be a bit of gratuitous cruelty. And all of us know that there is a point in the course of an illness at which nature herself mercifully dulls the mind and its power of grasping ideas begins to relax. In his Ingersoll Lecture on the Immortality of Man, given at Harvard some years ago, William Osler said that most people die as they were born, unconscious of what is happening. You doctors know this well. I have to tell my divinity students that this is so, and that at these times they are not to ask or expect anything like quick mental response to their ministry to the sick. These are not the occasions to carry on a prolonged discussion as to an afterlife.

In short this whole question of truth telling seems to me to depend upon the temperament and the mental state of a patient. No single categorical rule can be laid down; we have to trust our instinctive knowledge of human beings and be guided accordingly.

Prolongation of Life and Euthanasia

Regarding the first of these questions there seems to be little question. There is a point beyond which the mere artificial prolongation of the life of a body that seems marked down for death is not merely useless but also even an unkindness. One might even defend the thesis that it is a perverted conception of goodness and of ethics. When Shakespeare says, "She should have died hereafter," he meant, not that her death was premature, but rather that she was going to die some time and in any case.

When we are actually in sight of that time it seems to be right to accept the fact. I have never come across on the part of the laity any difference of opinion about the medical conduct of a case once this situation is accepted.

The question of euthanasia is more difficult. There is, as you know, much vocal medical opinion in its favor in England. And the matter is often discussed privately here. It is an open question. As to the act itself, many a suffering person has begged for it, many kinsfolk have been willing to accept it, and I suspect that many a doctor has been sorely tempted at this point. I have a friend who, with the connivance of her doctor, gave her husband, who was suffering from a cruelly painful and fatal disease, a heavy overdose of morphine. She said she had no scruples about doing so and had never had a single regret. You must know many more such examples than I know. She was either more resolute or more fortunate than most human beings. A few years ago I watched my Scottish terrier being put away. He was old and blind and sick. But even so I didn't like it. It seemed to me that the veterinarian and I were taking a great responsibility and one perhaps to which we were not morally entitled. How much more so in the case of a human life!

If euthanasia were ever to be legalized no single medical man could be or should be empowered to make such a decision alone. A panel of doctors would probably have to be set up by the state to make any such decision. Public medicine of any kind raises all sorts of valid questions. It is not easy to foresee a panel of state officials charged with this task, nor is it easy to envisage the doctor who would accept this responsibility as the major, if not the sole, form in which he practiced his profession. Whatever the warrant of a given emergency may be, the legal validation of euthanasia seems to cut against the whole basis and practice of medicine. I suppose that none of us are 100 per cent psychologically sound, and one wonders what perversions might creep into the practice of euthanasia.

Albert Schweitzer, who is a doctor as well as a minister, and who has done such splendid work at Lambarene in West Africa, says of himself that journeying up river from the coast to his hospital on one occasion he was searching for some basic ethical principle:

> Slowly we kept upstream, laboriously feeling for channels between the sand banks. Lost in thought I struggled to find the elementary and universal conception of the ethical which I had not discovered in any philosophy. Sheet after sheet I covered with disconnected sentences. Late on the third day at the very moment we were making our way through a herd of hippopotamuses, there flashed upon my mind, unforeseen and unsought, the phrase "Reverence for life." For all life.

His autobiography has many striking instances of his subsequent application of that principle.

This is, after all, the ethical basis of the practice of your profession as of my profession. If we forfeit that reverence we have slipped our moral moorings. And if in practice we violate that principle, we should know that we are doing so and take the responsibility for so doing. Once again, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To forsake one's own self is an act that leaves its scars on the mind. Personally, I should question the wisdom of medicine's accepting as a principle, and the state's legalizing in practice, acts of euthanasia. Such a *volte face* in the whole conception of the aim of the profession would impair the conscious integrity of its members and would introduce in place of an accepted principle — which, if it is ever to be violated, should be violated soberly and wittingly — a state of ethical perplexity and painful indecision in which each case must be decided on its own merits. The effect on the public would be almost disastrous, since it would introduce into these relationships a sense of insecurity and apprehension, rather than confidence and assurance. If a doctor or a minister has never had, or having had has lost, his reverence for life and his feeling for the sacredness of life, he lacks that which in theory his profession presupposes. Unless you and I are to revise radically our conception of our common task, it is not our business to take life, only to try to save it.

Rival Claims of Competing Individuals, or of the Concrete Individual and Society in the Abstract

We come, finally, to the specific type of problem that was proposed to me. Here is a woman apparently dying of an inoperable and incurable cancer of the stomach. She is being kept alive by blood transfusions, but the blood that she needs is the rarest type, of which the blood bank has only a limited supply. The transfusions cannot save her. Is it not foolish, perhaps even wrong, to waste this precious blood on her? Ought it not to be kept for some later patient who may be helped by it, whose life perhaps may actually be saved by it? Or here is a man in the iron lung, who could not live an hour outside it and yet may live half a lifetime in it, to the exclusion of someone else who might be got around a bad corner and in due time dismissed. Ought he to be allowed his monopoly of this mechanism?

These are difficult, even heartbreaking questions. Either way, the choice is a genuinely tragic one. I do not know that I have sufficient wisdom to answer them. I can only fall back on general principles.

There are two terms that have been much to the front in recent years. They represent what are called social trends. One is the word "depersonification," and the other the words "mass man." Both terms represent tendencies, particularly on the part of the state, to depreciate the value of the

single individual in favor of the group as a whole. These trends have found their fullest expression in countries where totalitarianism has been, or still is, the order of the day. In such societies the individual is of value only as a member of the mass, and is always regarded as expendable.

Our own country has just now fought two world wars in defense of the general idea of liberty and the rights of the individual. His liberties have had to be circumscribed in wartime, and now that the fighting is for the moment over, we are left with lives that are much less free, as far as our private affairs are concerned, than they were forty years ago. It could not have been otherwise, perhaps, and yet this steadily narrowing area in which anything like actual liberty and private initiative remains is one of the paradoxes of these years.

There is abroad a tendency to treat this doctrine of mass man as though it were a late discovery, the mature achievement of complex modern societies. I venture to point out that, on the whole, it is the oldest of all our social theories. It was the appraisal of life current in all primitive societies. The individual mattered only as a member of the tribe, and all the tribal rites looked to his initiation into the tribe and his subsequent identification with it. This was true of the religion of the early Israelites. The single individual had no independent worth either in his own eyes or for his fellows or even to Jehovah. The doctrine of the worth and moral independence of the individual emerges only with the prophet Ezekiel after the return from the exile. This lead is taken up and matured in Christianity, which holds that "not a sparrow falls to the ground without your Father." However difficult the doctrine may be to understand and defend, such is the doctrine of later Judaism and Christianity — both have traditionally believed in the value of the individual. Our social institutions come into being to express him and to defend him. "The Sabbath was made for man, not man for the Sabbath."

This appraisal of the facts was, also, the premise of all modern democracies, our own in particular. The case has never been theoretically proved beyond all contradiction, or vindicated in the total practice of any society. It remains, in many respects, a bold ideal. But unless we repudiate our hereditary faith, both religious and political, it is still our ideal, and its denial would mean a radical change in the whole temper of our life.

The drift of the times, in the worlds of finance and industry, and in military policy, seems to be in the direction of the dogma of mass man. At their hands the individual is inevitably more or less depersonalized. Perhaps it cannot be otherwise, given the numbers of human beings involved and the complexity of most modern issues.

In any case it is left largely to two groups of professional persons, the doctor and the minister, to vindicate a working faith in the value of the individual. Any lack of that faith on our part is tantamount to desertion of an ideal outpost that we have held in behalf of what we believed to be a valid cause.

The first social-settlement house in the English-speaking world, Toynbee Hall in East London, was presided over by a quiet little Anglican clergyman, Samuel Barnett. In her biography of her husband Mrs. Barnett says that any number of persons used to come down for a day from the West End of London to its dreary East End, with large blue-print plans for the redemption of those drab slums. They aired their plans, spent a pleasant evening with the warden and went away. Mrs. Barnett says that her husband came to the conclusion that the only permanent good ever done in the East End of London was done by those "who were willing to take time and trouble with individuals," and that this verdict upon the fact became his own rule of life.

A man who goes into the practice of medicine or of the ministry ought to enter his profession with that conviction and ought to do his best to vindicate it. There is a place in society for the man who wishes to devote his life to the general and all-over cause of public health. There is a place in the religious world for a man who feels he should sign on with one or another of the great reform movements of the time. The work of these men is necessary, and their contribution to society may be very great. But the practicing doctor and the parish minister are primarily concerned with individual human beings. The moment either begins to sacrifice his concern for the individual to some other hypothetical person, or to society in the abstract, he has mistaken his vocation.

He may justify his decision to himself on the grounds of a higher or broader loyalty, but he will have failed his cause at a point that it is more and more difficult to hold in the modern world. If he ceases taking time and trouble with a given individual on the ground that he can thus be of greater service to someone else he impairs to this extent the confidence of the community in himself and his profession. Once a man accepts the ministry of a parish he is under bonds to take time and trouble with the individuals who comprise it. Most of the failures that I know of in my own profession have been due to a neglect of that premise. If my analogy is valid I should suppose that once a doctor and a hospital have accepted a patient they are under bonds to see the patient through.

I agree that this may involve what will often seem a waste of precious time to no permanent good. But there is something more at stake here than the welfare of the single patient; there is also the confidence of the community in the integrity and single-mindedness of the profession itself. If

that confidence is impaired not merely the good name but also the actual effectiveness of the profession suffers in consequence.

These are tragic choices. And as Bradley says, the essence of tragedy is the fact of waste that it involves. To know them as tragic and to feel their tragedy is perhaps half the battle at the outset. If a man cannot feel these tragedies in medicine and the ministry there is something wrong with him. If he is a sensitive man he will feel them more deeply as the years go on. He will always make his decisions reluctantly and with pain of heart, if not perplexity of mind. But he is the defender in church and state of certain basic principles of our society that he cannot forfeit without radically revising the premises of his profession and to this extent impairing the whole tradition to which he belongs.

* * *

I have not answered Dr. Means's problems, or yours. But I have tried to point out what some of the issues are. In so far as I have any answers they are, briefly:

Tell the truth, but "tell the truth in love," and telling the truth in love may often mean silence rather than some hastily spoken word.

Maintain at all times a sense of the sacredness of life.

Be willing to take time and trouble with individuals at the expense of that abstraction known as mass man.

PROGNOSIS IN ESSENTIAL HYPERTENSION*

Eight-Year Follow-up Study of 430 Patients on Conventional Medical Treatment

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CONSCIENTIOUS interval evaluation of sympathectomy for essential hypertension by comparison with control material is progressively defining the limitations and the applicability of this procedure.[1, 2] The same attention to control material is required when one considers the usefulness of very restrictive diets, interest in which has recently revived.[3, 4] Before applying these diets generally and indiscriminately, we should ask ourselves what the remote effects will be on the body electrolyte economy, on work capacity and hot-weather tolerance, on resistance to infection, on the basal metabolism, on carbohydrate tolerance and on fetal health in pregnancy. Finally and practically, how often is an extremely irksome diet necessary in essential hypertension? If employed, does it actually prolong the life of the patient? Are most of the successes obtained in those patients likely to be matched in any case? To help answer these three important questions, adequate control material is the first necessity. This we believe we have and submit it herewith. In this series of cases, treatment consisted of the combination of physical rest and activity deemed appropriate for each patient, sedative drugs and sometimes sulfocyanates, low-fat, relatively high-protein and low-salt diets, in exceptional cases low-sodium diets for short periods, the usual drugs for congestive or anginal failure and finally practical psychotherapy.

Originally, our series of patients with hypertension consisted of 1072 patients personally observed, the great majority of them between 1935 and 1940. After patients with transient nervous hypertension, those with glomerulonephritis, those who were sympathectomized and those inadequately followed had been excluded, 646 subjects remained. Observation comprised a careful history and physical examination, routine blood and urine examinations, a fractional intravenous phenolsulphonephthalein test, a urine concentration test, frequently intravenous urography or orthodiagram or seven-foot film of the heart and an electrocardiogram.

After the original observations and satisfactory follow-up study, these 646 patients were classified according to clinically recognizable organic changes in the three vital areas: the head, the heart and the kidneys. The classification depended upon the most marked change in the area or areas in which it was found. These criteria are presented below.

CLASSIFICATION

Grade I Changes

These patients have no changes or minimal changes in the fundi as represented by narrowing

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of the arterioles, normal hearts or no more than prominence in the region of the left ventricle by x-ray study, no impairment of renal function by the tests used and normal urine examination or occasionally slight albuminuria and slight changes on microscopical examination of the sediment.

Grade II Changes

These cases include moderate organic changes in the fundi as represented by widening of the arteriolar light reflex, narrowing, caliber changes and arteriovenous compression. The heart exceptionally is normal by x-ray study and is usually prominent in the region of the left ventricle and sometimes more definitely enlarged but without functional impairment; the kidney is normal, slight degrees of albumin and minimal numbers of formed elements are found in the sediment, or there may be slightly impaired function.

Grade III Changes

The fundi are rarely normal, usually showing arteriolar narrowing, caliber changes, wide light reflex and arteriovenous compression. Often, there are exudates and hemorrhages; the heart is often moderately to markedly enlarged, commonly with symptoms and signs of actual or impending congestive failure or symptoms of anginal failure. The urine frequently shows albuminuria and casts, and renal function is often impaired though actual failure (uremia) is not common; cerebral accidents sometimes occur (in 20 per cent of cases).

Grade IV Changes

The cardinal — indeed, the obligatory — sign is edema of the optic disks, with or without exudates and hemorrhages and always with marked narrowing of the arterioles. Cardiac enlargement and congestive failure may be present; renal impairment and failure are common.

It is emphasized again that classification is not based on one organ, such as the fundus, but on recognized changes in any area, and that the classification is: mild (Grade I), moderate (Grade II), or severe benign (Grade III), according to the most advanced change, whether in one or more areas. For instance, a patient who has had a cerebral thrombosis is placed in Grade III, though the heart, kidneys and fundi are normal; no classification higher than III is made if the kidneys are impaired, there is angina pectoris, and there are exudates and hemorrhages in the eyegrounds — that is, there may or may not be evidence that one or all vital areas are affected seriously. Grade IV or malignant hypertension is recognized by papilledema alone with or without other changes. In 95 per cent this sign indicates a rapidly progressive course to a fatal outcome. In Grades I and II patients must be observed a year or more for one to be sure that the course characteristically is progressing slowly, if at all. In Grade III serious change is promptly recognized in fundi (exudate or hemorrhages, or both), in the cerebral circulation (thrombosis or hemorrhage), in the heart (marked enlargement, actual or impending congestive or anginal failure) and in the kidneys (significant impairment of function).

We are well aware that the outward signs are poorly correlated with the inward state in essential hypertension as in other aspects of man, but we must use the signs that we have. For this reason, any clinically observable sign of vascular change in one or more of the three vital areas is taken as indicative of diffuse vascular disease, however localized such a change may be on clinical examination. It is further assumed that the severity of recognizable organic change as defined in the classification is directly proportional to the severity of the disease process. The latter assumption in practice has proved fairly correct.

In 1942–1943, after an average four years of follow-up study of 50 per cent of the 646 cases, the mortality was 6 per cent in Grade I hypertension, 17 per cent in Grade II, 36 per cent in Grade III, and 80 per cent in Grade IV.[1] In 1946–1947, after another four years, 430 cases, or 66.5 per cent of the 646, were followed. The mortality was 22 per cent in Grade I, 47 per cent in Grade II, 78 per cent in Grade III and 94 per cent in Grade IV. It is evident that this clinical classification of essential hypertension on the average indicates the severity of the disease in respect to survival.

The average and median duration of known hypertension in each grade of the 430 patients is given in Table 1. The known duration of hypertension in Grades I to III is longer in the living (twelve to fifteen years) than in the dead (seven to nine years) patients. This reminds us of three things: that the actual onset of hypertension is hardly ever accurately determined; that the prognosis varies with age and sex; and that present methods of clinical examination as employed by us differentiate patients who do well from those who do badly only by an average of each grade and not in an individual patient. In Grade IV hypertension 3 patients with papilledema have survived an average of nine years and two months. These cases are exceptional. Others have had a similar experience.[5, 6] The average duration in patients with Grade IV changes who died is three and one-fourth years, owing to the long duration of apparently benign hypertension terminated by the malignant phase in some of these cases. The median known duration is just under one and a half years. The average duration of our own observation of these patients is a little over seven months, and the median slightly more than four months. It is almost always apparent at once that the course of the disease in patients with Grade IV changes is intense and rapid. It is usually apparent in Grade

III that one is observing an end stage of a condition that has often been very slowly progressive. In Grades I and II a number of interval observations of a year or more are needed to prove that the condition is slowly progressive or stationary. We know of no infallible signs at a single examination in these patients with Grade I and II changes that will foretell the appearance of late Grade III or malignant Grade IV changes.

The age distribution of the various grades is shown in Figure 1. By inspection, one can notice that the patients with Grade IV changes are younger than all the others and that those with Grade II and III changes are older than those with Grade I. This suggests that Grade I, II, and III changes form a group of patients that represents a condition different from that of Grade IV.

Table 2 shows the sex distribution and survival rates and demonstrates that in this sample there are more female than male patients with essential hypertension. In Grades I and II the percentage of women is greater than that of men. The reverse is true of Grade IV. In Grade III the numbers are equal, but the percentage of the total number of each sex reveals 50 per cent men and 40 per cent women with this degree of hypertension. In Grade IV the percentage of the total number of each sex reveals 17 per cent men and 9 per cent women. This sex difference is considered significant statistically, suggesting that female patients tend to have the milder grades of this disease. It is an important point also that the probability of survival for females is definitely superior — 82 per cent as compared with 66 per cent for the men in Grade I, and 57 per cent as compared with 42 per cent for the men in Grade II. The probability of survival is somewhat better in Grade III (27 and 17 per cent for female and male patients, respectively) and also better in Grade IV (9 and 3 per cent each for female and male patients).

The onset and progress of organic change in essential hypertension is assumed to depend upon the duration, the persistence and the height of blood pressure. To evaluate the factor of age, the age at first known hypertension was calculated, and Grades I to III were grouped as follows: twenty-nine years or less, thirty to thirty-nine inclusive, forty to forty-nine inclusive, and fifty or over. The mortality and the average duration of known blood pressure were determined for each group. This was not done in Group IV because the course of the disease was short at any age. The results for Grades I to III for the different age groups are shown in Table 3. In these mortality figures, deaths from causes other than hypertension are excluded.

From inspection of these figures it appears that an increase in age is associated with a higher mortality only in Grade I hypertension. In Grades II and III the patients are older. The numbers in age group twenty-nine or less are too few to be significant. It is assumed that the course of the disease in many patients in Grades II and III when they were first seen was already more advanced. The usually shorter known duration of hypertension in the dead patients may have been due to the cir-

TABLE 1. *Average and Median Duration of Known Hypertension by Grades.*

Grade of Hypertension	Duration	
	Average	Median
	yr.	yr.
Living patients:		
I	12.5	11.5
II	13.9	13.0
III	14.7	13.0
IV	9.2	—
Dead patients:		
I	9.1	8.5
II	8.6	7.0
III	8.2	7.0
IV	3.2	1.4

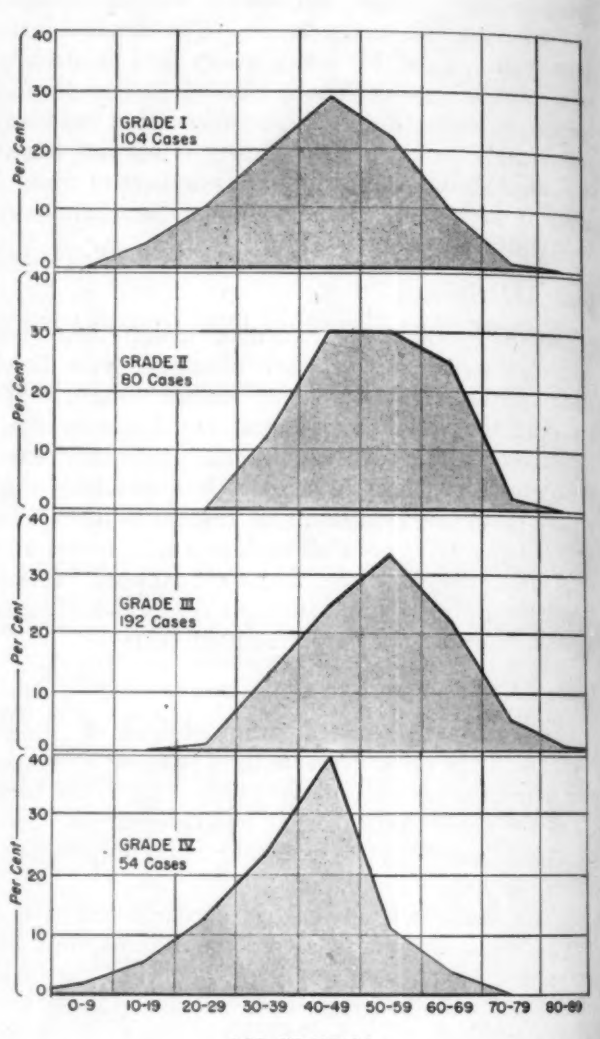

FIGURE 1. *Age Distribution by Decades.*

cumstance that an earlier asymptomatic stage of the disease passed unnoticed. It may be that variations in the natural course of hypertension are due to constitutional, infectious, dietary, situational,

TABLE 2. *Sex Distribution and Survival Rates.*

Grade of Hypertension	Status of Patient	Male Patients		Female Patients	
		No.	Survival %	No.	Survival %
I	Living	25		56	
	Dead	13		10	
	Totals	38	66	66	82
II	Living	11		31	
	Dead	15		23	
	Totals	26	42	54	57
III	Living	16		26	
	Dead	80		70	
	Totals	96	17	96	27
IV	Living	1		2	
	Dead	31		20	
	Totals	32	3	22	9
All grades	Living	53		115	
	Dead	139		123	
	Totals	192	28	238	48

psychologic or other unknown factors that influence its progress favorably or unfavorably.

We wish to form an estimate of the prognosis of essential hypertension treated by conventional medical management based on the observation of these 430 patients followed in some cases for as long as seventeen years, some of them for shorter

TABLE 3. *Mortality and Average Duration of Hypertension according to Age at Onset.*

Age	Mortality	Average Duration	
		Living patients	Dead patients
yr.	%	yr.	yr.
Patients with Grade I changes:			
29 or less	12.5	12.5	14.0
30–39	12.0	12.8	9.0
40–49	19.0	11.1	6.2
50 and over	40.0	13.3	9.7
Patients with Grade II changes:			
29 or less	—	20.0*	—
30–39	44.0	15.4	14.1
40–49	48.0	11.4	8.9
50 and over	42.0	11.9	6.6
Patients with Grade III changes:			
29 or less	82.0	—†	11.3
30–39	78.5	15.6	8.7
40–49	68.0	15.8	9.1
50 and over	80.0	11.3	6.9

*Includes only 6 patients.

†Only 2 living patients, both of whom are included under group 30–39 years of age.

periods, the average being eight years, and many of them with known hypertension long before our time of observation. We have taken the 104 Grade I patients, the 80 Grade II patients, the 192 Grade III patients and the 54 Grade IV patients as 100 per cent in each grade and plotted the survival rate in per cent after four years, and again after eight years (Fig. 2). The curve for Grade IV has been drawn with a steeper slope than is apparent from the four-year follow-up study. The reasons for this are that the median duration of known hypertension in this group is about one and a half years and that the median duration of our observation of this group prior to death is only slightly more than four months. If the follow-up examination had been made at two years instead of at four years, we should probably have found just a trifle larger percentage of survivors, as in the patients examined after four years.

Tentatively we have used a method of prediction that is both rough and speculative, by which one

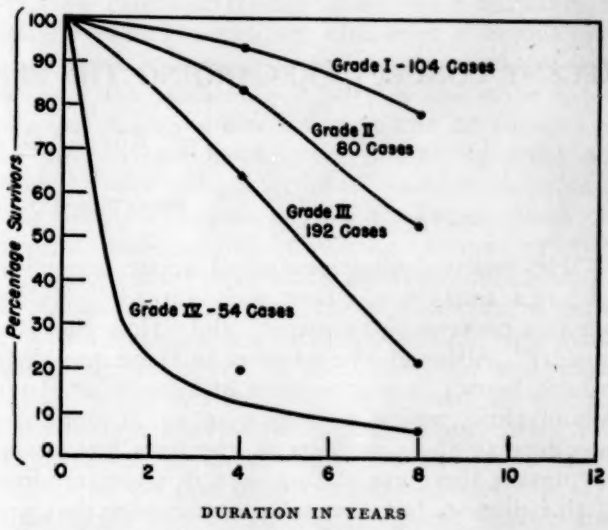

FIGURE 2. *Survival according to Duration of Hypertension.*

might estimate the probable percentage of survivors at twelve years in Grade I as 58 per cent, in Grade II as 24 per cent, in Grade III as less than 2 per cent and in Grade IV as almost zero. Three years hence we hope to have the actual percentages.

Discussion

From our data, the quickest and clearest demonstration of the effectiveness of any therapeutic program will be to show survival of 20 per cent or more of a significant number of patients with Grade IV or malignant hypertension for five or more years. This criterion has been satisfied by Peet's[7, 8] experience with dorsal sympathectomy.

The next most definite criterion of effectiveness of any given program will be to demonstrate the survival of two thirds of a significant number of patients with Grade III hypertension for more than five years.

The therapeutic effectiveness of any program in Grade I and Grade II hypertension will be doubtful until a significant number of patients have been

followed for ten years. At present we may say that considerably more than 80 per cent should be surviving after eight years in Grade I, and 60 per cent or more in Grade II to demonstrate therapeutic superiority. Consideration should be given to the sex incidence in these two grades, and allowance made for the uniformly better prognosis in female patients.

We urge that responsible clinical investigators interested in the study of essential hypertension agree upon terms and criteria for a clinically applicable classification of hypertension for the purpose of establishing the prognosis and the effectiveness of treatment in this, one of the most serious threats to life of civilized man.*

*The classification here used is based on that of Keith, Wagener and Kernohan,[9, 10] whose work in this field since 1920, particularly in establishing the clinical syndrome of malignant hypertension, is gratefully acknowledged.

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RECENT CONCEPTS REGARDING THE SPREAD AND TREATMENT OF POLIOMYELITIS*

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THE essential questions asked about poliomyelitis today are, "How is it spread?" "How can you prevent the disease?" and "How can you cure it?" Although the answers to these questions are not known, a vast amount of knowledge about poliomyelitis, which is beginning to fit together, may furnish these answers in the next few years. At present there are glaring gaps in understanding of this disease, but the definite advances that are being made are filling some of these gaps.

Epidemiology

Poliomyelitis is a worldwide disease affecting all races and classes of people. It is recognized to be most important as an epidemic disease, however, in North America, the Scandinavian countries, Great Britain and elsewhere in Europe. Until recently it was assumed to be very uncommon in the other sections of the world. Recent investigations by Paul et al.[1, 2] have shown that, although epidemics of paralytic poliomyelitis are uncommon in the countries of the Middle East and the Far East, nonparalytic and nonepidemic infections are probably widespread in these and similar countries. This was clearly brought out by the experience of British and American troops stationed in the Middle East and Far East respectively. For, although there were only a few cases of poliomyelitis recognized in the native populations, the incidence of poliomyelitis among the foreign military personnel was significantly higher than that in their home countries.

It is noteworthy that recognized epidemics are of recent occurrence and date back little more than sixty years in this country and in Scandinavia. During this period the age incidence of recognized cases has changed. Whereas the disease primarily involved infants and young children at first, there was a gradual extension into the older age groups here and in Scandinavia after the passage of years. Japan, on the other hand, had its first large epidemic in 1939 and, interestingly enough, is having the same younger age incidence that was seen in the early epidemics in the United States. Ninety per cent of the cases reported in Japan were in children under five years of age, whereas only 36 per cent of the patients were under five years in recent epidemics in this country.[1] It seems that there is a higher immunity in the older age groups in these native populations than is apparent in the population of the United States. This can be attributed to a more widespread dissemination of the virus in infancy in these countries, which, with the lower reported incidence of the disease, are also the countries of poor sanitation, so that it has been postulated that poor sanitation leads to wide dissemination of poliomyelitis virus among the young infants, which is not attended with a high rate of paralysis. On the other hand, as a country's sanitation is improved, it seems that more persons escape exposure to the virus in the early years and therefore remain

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susceptible to a later and possibly more serious infection.

The spread of poliomyelitis from patient to patient may go on by different routes. It is possible to infect experimental animals and presumably man through three routes: the nose and olfactory bulbs; the skin; and the gastrointestinal tract. It is well accepted that the usual and almost exclusive mode of entry in man is by the oropharynx through the mouth or nose. Virus leaves the human body by two routes, the oropharynx and the lower intestinal tract in the feces. Oropharyngeal swabbings contain virus in as many as 50 per cent of patients, especially for two to three days before the onset of the clinical disease to three to five days after the onset.[3] Stools have been found to contain virus in an even higher percentage of cases, especially in the first two weeks of the disease, but also as long as nineteen days before clinical evidence of infection[4] and six weeks or longer after the onset of disease in some cases.[5] The possible pathways of the virus from the oropharyngeal secretions or feces of the apparently healthy carrier or the clinical case to the new, susceptible person are shown in Figure 1. Virus may be transmitted directly by

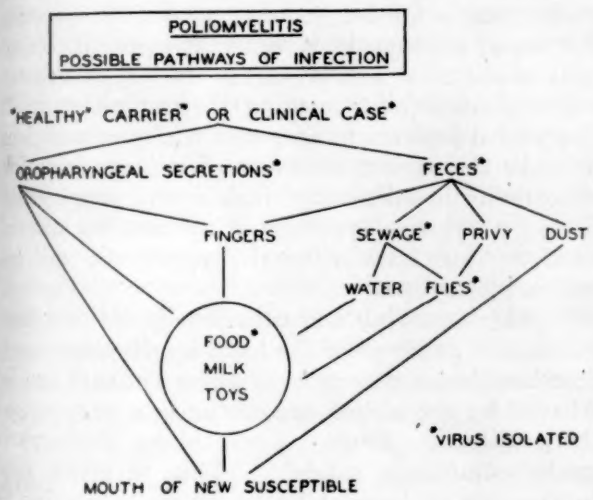

FIGURE 1.

inhalation and ingestion of infected oropharyngeal droplets. Infected oropharyngeal secretions may also be passed by means of fingers and toys or food during the intimate play of children. Fecal virus may be transmitted directly as fecal dust or through the medium of toys among children, just as pinworm ova are spread so widely. Direct fecal contamination of food, including milk, may occur in the same way that typhoid spreads from a carrier, or fecal contamination of food or water may occur indirectly, transported by flies from exposed feces in privies or toilet bowls or from contaminated sewage. All these routes and others are possible and even probable, but there is no agreement on which one is the most important in the actual transmission of the disease. The marked summer incidence of the disease and the finding of the virus in pools of flies caught during epidemics make the theory of fly transmission very attractive. I believe, however, that the fly plays only a minor role.

At present, the most convincing evidence indicates that close contact between human carriers of the virus plays the important role. During any epidemic only a small percentage of people carrying the virus are recognized since the vast majority of carriers do not have a typical illness. There is a serious lack of an easy and economical epidemiologic tool, such as the serologic tests for syphilis or the skin test for tuberculosis, that will pick up these inapparent infections. However, there are several small studies that show the importance of contact. Brown, Francis and Pearson[4] studied a boy's camp in Detroit after the appearance of poliomyelitis in a camper. One week after this case, they found poliomyelitis virus in the throat or feces of 5 of the remaining 7 boys in the same cabin, whereas no virus was found in the 10 boys living in the next cabin. Another interesting point was brought out — namely, that nineteen days later one of these boys carrying the virus developed typical poliomyelitis following severe exertion. A similar study was done by Gear and Mundel[6] in Johannesburg. After the appearance of paralytic poliomyelitis in a two-year-old child they tested the other members of the household and found virus in the stools of an eight-year-old brother. Twelve days later he developed poliomyelitis. Subsequently 2 children whom he had visited just before he became ill developed poliomyelitis, and their father had the virus in his stool. These 3 children and 12 others were at a birthday party together; of this group tests on 8 subjects revealed that 5 were harboring the virus. One of these carriers had an illness compatible with nonparalytic poliomyelitis. In summary, 1 paralytic case was followed by 3 other paralytic infections, 1 nonparalytic infection and 5 carrier states among 14 healthy contacts tested. Casey and his co-workers[7] have carried out extensive studies, also pointing out the importance of contact.

From these studies one can conclude that poliomyelitis virus has a world-wide distribution; that clinically recognized epidemics of poliomyelitis infections are of relatively recent origin and have been particularly prominent in the countries with high sanitation (this may mean that in countries of poorer sanitation, infections are occurring in the younger age groups with resulting immunity, but not associated with the usual signs of poliomyelitis); that close personal contact between apparently healthy carriers or clinical cases and susceptible hosts plays an important role in this widespread dissemination of the virus; and that

something happens during the summer in the temperate zones to increase this dissemination of virus (this may be explained by insect transmission, but other possibiiities such as changes in the host or the virus itself may prove to be more important).

Prevention

The epidemiology of poliomyelitis is important, for it leads to a discussion of prevention. The first approach is to try to prevent the dissemination of the virus. Although the most important pathway of infection is not known, the foregoing discussion suggests certain steps to minimize the transfer of the virus. Ordinary contact in schools, movies and churches may play some role, but intimate contact between children during epidemics appears to be the most dangerous factor in the spread of the virus, and should be reduced to a minimum. Foods commonly eaten raw should be washed, and all milk should be pasteurized. In addition, the possibilities of transfer of virus by flies should be minimized by fly-abatement programs and screening of all food in stores, restaurants and kitchens. Screening flies away from exposed feces in privies and toilets should be done, and further studies should be encouraged on ways to inactivate the virus present in sewage.

The second approach is to try to reduce the number of paralyzing infections among susceptible persons who have become carriers of the virus. There is evidence that exhaustion, severe chilling, coincident gastrointestinal infections and operations on the nose and throat may make the difference between a carrier state, or nonparalytic infection, and a case of paralysis. For this reason these conditions should be avoided during epidemic periods.

The third approach is to produce artificial immunity to poliomyelitis. Because of ignorance of the exact mode of transmission of the virus and because of the practical difficulties of applying what is known about it, the immunization of children against poliomyelitis is the greatest need in this field. Attempts in the past have met with failure either because the vaccines used did not produce immunity or because they were too dangerous by reason of containing live virus. New approaches to this problem are being made, and a satisfactory vaccine may be developed. If it can be proved that the people of the more unsanitary countries actually acquire immunity without demonstrable infection from exposure to the virus in early infancy, this may lead to an immunization procedure by the oral administration of virus. This idea has appealed to many people, but obviously it cannot be undertaken lightly.

Treatment

The treatment of poliomyelitis is still hampered by the lack of a specific viricidal agent. The temporary popularity of serum from convalescent patients has waned, and few people believe that it has any beneficial effect. In the present state of ignorance the treatment resolves itself around nonspecific measures aimed at the relief of complications during the acute stage, making the patient comfortable, limiting spasm and contracture of the muscles, muscle re-education and the correction of resulting deformities.

Almost all the deaths from poliomyelitis are due to bulbar or respiratory involvement so that improved treatment for this form of the disease is particularly important. Some of these deaths have resulted from complicating pneumonia, which may be prevented or treated by the judicious use of chemotherapy or antibiotic therapy (sulfonamides, penicillin). The early recognition and treatment of atelectasis may prevent some of the deaths. A more recent development is the early use of tracheotomy and oxygen therapy in selected cases described by a team of workers at the University of Minnesota,[8] who have shown that many patients with bulbar involvement have difficulty getting a good respiratory exchange even in the respirator. By the use of tracheotomy, alone or in conjunction with the respirator, and by the liberal use of oxygen they believe that they have pulled many patients through who would otherwise have died. Their criteria for tracheotomy were: "Respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor; excitement and unmanageability causing the patient to resist pharyngeal aspiration; stupor of a degree sufficient to make the patient oblivious of the accumulation of secretion in his airway; inability to cough effectively; pharyngeal pooling of mucus, vocal cord paralysis (or intralaryngeal hypesthesia demonstrable by laryngoscopy)."[9]

Another annoying and occasionally serious complication is paralysis of the bladder. Recent experience has shown that most of these patients can be relieved by the use of one of the new parasympatheticomimetic drugs, furmethide (furfuryltrimethylammonium iodide).[10] This is given subcutaneously in doses of 1.5 to 5.0 mg. according to age, and is usually followed by voiding in five to ten minutes. The drug may have to be repeated, but spontaneous voiding is usually re-established after the first dose. In a short series of cases it has been found that catheterization, with its discomfort and attendant danger of urinary infection, can be avoided in the majority of cases.

The main treatment of poliomyelitis is symptomatic and at present is usually some modification of the Kenny technic. It is not necessary to dwell on Miss Kenny's theories regarding the therapy that she has gradually evolved, for these theories are not accepted as being tenable.

It has been pointed out that all her therapeutic measures of positioning in bed, hot applications and early muscle re-education have been described

before and used extensively in one clinic or another. It is not fair to Miss Kenny, however, to claim that nothing is new in her scheme of treatment, for it is quite apparent that these methods had given way in previous years to prolonged immobilization in splints or casts, followed by late muscle re-education. A few physicians never adopted the prolonged use of casts and splinting, but the majority had done so before Miss Kenny's appearance. Now very little of this type of immobilization is being practiced.

The chief differences in the Kenny regime and so-called "orthodox" treatment are that muscle re-education, including passive motion of the extremities, is started earlier in the Kenny program; that immobilization is much more complete in the "orthodox" method; and that Miss Kenny treats contractures by application of heat and tendon stretching rather than by corrective appliances.[11, 12]

There are many minor variations in the technic of treatment, of course, but it does not seem that many of them are important. Many different methods of treatment between these two extremes have been used for the past thirty years. Some men carried out a program of treatment very similar to Miss Kenny's for years before her advent. At the present time most medical centers have adopted treatment schemes that are very similar to the Kenny method, without its rigid barriers to modification.

It is of interest to compare, if possible, the results of treatment by these various methods. One cannot be dogmatic about such a comparison, for each investigator has a different method of evaluating results. However, a review of all the available articles that include specific figures shows very similar therapeutic results. Mortality rates over the past thirty years have varied, and there has been some variation in end results, but there appears to be no really significant difference in results obtained by the various methods.[13]

The first fairly satisfactory statistics from the Kenny Institute fail to prove any superiority for this method of therapy. I for one, however, would not go back to the period of long immobilization in casts. It is impossible to agree with Miss Kenny's pseudoscientific reasoning, but it does seem that her method of treatment is more comfortable for the patient and probably makes the recovery of muscle function easier, since the peripheral tissues are kept in better tone.

The only other new developments in therapy during the past few years have been the use of prostigmine and curare for the relief of muscle spasm. In the absence of proved value the latter is too dangerous for use at the present time, although it does warrant further study. The value of prostigmine also is not well proved. Because of the variability of this disease, many better controlled studies will have to be made before one can assess the worth of either of these drugs. Fortunately, most children with poliomyelitis will escape paralysis regardless of the method of treatment employed, and even those who are paralyzed will improve their muscular co-ordination and efficiency if treated over long periods by experienced personnel.

Conclusion

In conclusion it may be noted that the picture is confused, but it is getting clearer. Newer theories regarding epidemiology, prevention and therapy have the support of well controlled clinical observation and experimentation. The outlook is better already, and investigators may well be on the brink of new discoveries that will allow conquest of this disease.

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LIPEMIA IN HEMOCHROMATOSIS*

Report of a Case

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THE occurrence of lipemia in hemochromatosis has not been described in the literature, to our knowledge. The recognition, therefore, of an opaque serum taken from an otherwise typical patient in the fasting state was quite surprising. But so are several variants of hemochromatosis reported since Trousseau's first casual allusion to this syndrome in 1865.[1] For example, of the

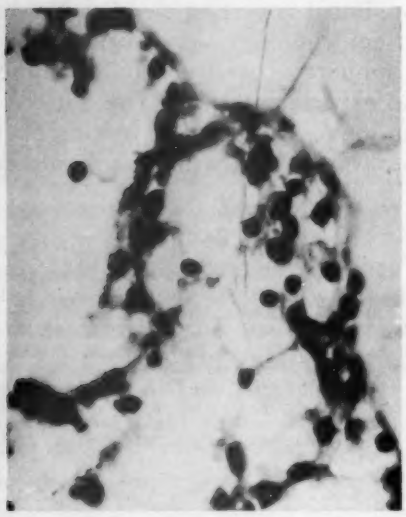

FIGURE 1. *Section of Bone Marrow Aspirated from the Iliac Crest, Showing Increased Amounts of Hemosiderin in Reticular and Sinus Epithelial Cells (High-Power, Hemosiderin and Eosin Stain).*

triad of cirrhosis of the liver, diabetes mellitus and pigmentation, cirrhosis only seems to be constant. In some cases diabetes has been proved not to have been present.[2, 3] Others[4] have been unable to demonstrate intradermal pigment, despite apparently typical pigmentation. Moreover, the pathological physiology itself is obscure. One salient fact stands forth, however: these patients do retain abnormal amounts of iron salts.[5] Sheldon[1] has estimated that the total iron content in hemochromatosis may lie between 25 and 50 gm., as compared with a normal of approximately 3 gm.

Up to the present, figures seem to matter little. Those for the increased serum fat in this case are readily available. So far as they might indicate etiology per se, they are of as much aid as those for the total iron content would be. The present circumstance, however, does give occasion for careful reconsideration of the causes of postabsorptive lipemia.

CASE REPORT

A 56-year-old fireboat deckhand was admitted to the hospital in July, 1947, with the chief complaint of failure to gain weight. Diabetes mellitus had been diagnosed 18 months previously, after he had noted polyuria for 8 weeks. These symptoms were accompanied by a 30-pound weight loss. His physician had placed him upon 35 units of protamine insulin daily. No change in weight had followed this regimen. Four months before admission, he had entered another hospital because of painful feet and nocturia. Hepatomegaly, diabetes and pigmentation had been noted by a medical student acting as a subintern. Roentgenograms of the legs had revealed a moderate amount of arterial calcification and mild osteoporosis of the bones of the feet. The first fasting blood glucose had been 211 mg. per 100 cc., a cephalin flocculation test had been ++, and the fasting serum collected

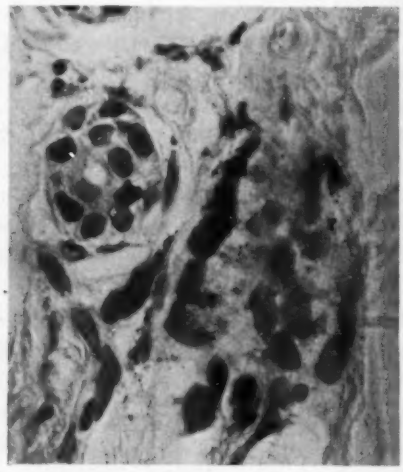

FIGURE 2. *Sweat Gland from the Dorsum of the Hand, Showing Hemosiderin Granules within the Basement Membrane (High-Power, Ferrocyanide Technic).*

for an icteric index was reported as "too cloudy" for determination. He had remained on 35 units of protamine insulin until he was admitted for evaluation of the diabetes and other studies.

The patient related that while in high school he had been nicknamed "Gypsy"; that he had frequently used argyrol swabs for "colds"; but that his skin had become distinctly darker during the onset of overt diabetes. Since the insulin had been started he had regained much of his former strength, there was no nocturia, and his feet had improved. He had had loss of libido and potency for 18 months. He denied alcoholism. The family history was suggestive of hemochromatosis in that his mother had also been dark skinned, but she had died at 75 years of age. His brother, killed acci-

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dentally at the age of 44, was the darkest of the family, but so far as is known he was not diabetic.

Physical examination revealed a bronze-gray cast of the exposed areas, the unexposed portions showing merely a peculiar dirty-blue pallor. The scleras were white. The mucosas were normal. The retinas were not remarkable. Occasional extrasystoles were noted, but the heart tones were of good quality. The liver was firm, smooth and nontender. It was enlarged four fingerbreadths and presented a rounded edge. The tip of the spleen was palpable. Angiomas and xanthomas were not present. The axillary and pubic hair were normal, but the genitalia showed mild atrophy. The rectal sphincter tone was good, and the prostate normal. Pedal pulses were present.

The blood pressure was 120/80.

The laboratory procedures are best enumerated as functional groups:

Hepatobiliary system. The albumin-globulin figures were 3.8:3.2. gm. The alkaline phosphatase was 10.2 Bodansky units. The cephalin flocculation was ++++, and the thymol turbidity, 0 units. The prothrombin time was normal. The bromsulfalein test, 5 mg. per kg. of body weight per 45 minutes, showed about 10 per cent retention of the dye (serum, opaque); the total cholesterol was 208 mg., and the cholesterol esters, 68 mg. per 100 cc. The total serum lipids were 1057 mg. per 100 cc., and the lipochrome index, 2.6 units. A Graham–Cole test showed nonvisualization of the gallbladder after the administration of nine "priodax" tablets. Duodenal drainage then revealed normal "A" bile, but "B" bile could not be obtained.

FIGURE 3. *Liver Needle Section, Showing Hemochromatotic Cirrhosis (Low-Power, Hemosiderin and Eosin Stain).*

Pancreas. Pancreatic lipase and amylase were present in normal amounts in the duodenal contents; the stool fat and fatty acid content was not abnormal (Sudan III). Fatty acid crystals were not seen, nor were undigested fibers observed.

Kidneys. Urinalysis showed a trace of protein, but no formed elements. The urine concentration reached 1.015 after 15 hours' abstinence from fluids. The phenolsulfonephthalein excretion after adequate fluids was 40 per cent in 15 minutes, and totaled 50 per cent at the end of 2 hours. The serum phosphorus was 3.6 mg., and the blood urea nitrogen, 14 mg. per 100 cc.

Adrenal glands. The serum sodium was 318 mg., and the serum potassium, 11.4 mg. per 100 cc. A Kepler–Power water test[6] showed a night volume of 280 cc., the largest hourly day specimen measuring 90 cc. The quotient, however, was 30 according to Procedure II and, therefore, negative.

FIGURE 4. *Portion of the Liver Needle Section, Showing Hemosiderin Granules within the Liver Cells, the Bile-Duct Epithelium and the Fibrous Stroma (High-Power, Ferrocyanide Technic).*

Hematopoietic system. The hematocrit was 40 per cent. The red-cell count was 3,800,000, and the hemoglobin 11.2 gm. (photometric technic). No macrocytosis was evident. The gastric contents were acid after histamine. Bone-marrow smears obtained from the iliac crest showed a marked increase in erythropoiesis, mild myeloid maturation arrest and hemosiderosis of fixed cells. Pathological sections of the clotted marrow showed that it was moderately fatty. Increased amounts of hemosiderin were present within the reticular and the sinus epithelial cells (Fig. 1).

A skin biopsy obtained from the dorsum of the hand revealed slight to moderate amounts of hemosiderin about the sweat glands (Fig. 2).

Liver needle biopsy showed a well established portal cirrhosis with moderate bile-duct proliferation. Abundant pigment was present within the fibrous stroma, and smaller amounts were found within the hepatic cells proper, as well as within the bile duct epithelium (Fig. 3 and 4). No active degenerative changes were evident.

The hemosiderin present in all three locations exhibited the ferrocyanide reaction characteristic for this pigment.

Discussion

The clinical picture in this case was sufficiently characteristic to make its discussion unnecessary. The lipemia, however, warrants some consideration. Since it most probably reflects primary digestive-organ impairment, the interrelated functions of the liver, the pancreas and the gastrointestinal tract are involved to a variable degree. Of course, lipemia is a feature of the nephrotic syndrome, but this need not be considered here.

The gastrointestinal tract is probably not at fault. This is a postabsorptive lipemia. As such, it is somewhat more logical to assume that this mani-

festation reflects an inadequacy of assimilation rather than excessive absorption. Before assaying the contributory roles of the liver and the pancreas, however, an examination of the physical and chemical characteristics of this lipemia may be helpful.

The term "lipemia" as it is used here is a clinical one — that is, it refers to visible amounts of fat in the fasting serum or plasma. The opacity is due to fats in their neutral phase. According to Thannhauser,[7] this is usually but not necessarily always accompanied by hypercholesteremia. Conversely, markedly elevated serum cholesterol and phospholipid levels are exhibited in the perfectly transparent serums of patients with primary biliary "xanthomatous" and cholangiolitic types of cirrhosis. These patients do not have lipemia, however, for their neutral fats are normal in amount. In this case excess neutral fats were not accompanied by an increase in either phospholipids or cholesterol (Table 1).

This fat pattern is a key consideration. It immediately eliminates idiopathic hyperlipemia,

TABLE 1. *Serum Fat Analysis.**

	PATIENT	NORMAL CONTROL
	mg. per 100 cc.	*mg. per 100 cc.*
Total fatty acids	599	200–400
Neutral fat	370	0–150
Total phospholipids	151	150–250
Total cholesterol	219	150–260
Cholesterol esters	139 (64%)	70% of total

*Reported through the courtesy of Dr. Siegfried J. Thannhauser, of Boston.

which is characterized by elevated cholesterol and phospholipid levels, in addition to the high neutral fats shown here.

The liver, moreover, is apparently not the prime mover in this lipemia. For although previous laboratory data had shown hepatic dysfunction, the essentially normal phospholipid, cholesterol and cholesterol-ester relations indicated that the hepatic phase of fat metabolism was unremarkable. Man et al.[8] concluded from similar fat studies that a "hypolipemia" usually exists in cirrhosis. The neutral fat seldom exceeded the upper limit of normal, the cholesterol and lipid phosphorus were either normal or decreased, and the cholesterol esters were often decreased. Aside from the pigment present in this liver, the process here is identical with that in Man's cases, and should not per se produce a hyperlipemia of this type. Although some of Thannhauser's cases exhibited mild elevations of neutral fat, these apparently occurred with depressed hepatic function, as shown by manifestly poor cholesterol esterization. Such a depression of function was not observed in the case reported above.

The pancreas, however, may be responsible for this lipemia, by virtue of either islet-cell or even acinar-cell dysfunction. Primary diabetes under control should not logically produce a persistent postabsorptive neutral hyperlipemia. Man and Peters[9] concluded that "abnormalities of the serum lipoids are related loosely, if at all, to diabetes." When lipemia and hypercholesteremia did occur, these could not be correlated with the "inherent severity of the (islet cell) disease as measured by any recognized criteria." Alloxan diabetes in rabbits[10] and in dogs,[11] moreover, when controlled by insulin, failed to produce a hyperlipemia (total serum lipids). But high lipids and cholesterol accompanied fatal alloxan diabetes in all of Kendall's[12] animals.

The patient in the case reported above is a "fragile" diabetic. On 50 units of protamine zinc insulin daily his blood glucose levels have always been low (less than 100 mg. per 100 cc.), with rather high postprandial values (more than 240 mg. per 100 cc.) and glycosuria. There has been no ketosis, however, and the transiently elevated glucose levels should not furnish cause for this lipemia. He has never exhibited clinical shock. Islet-cell diabetes, therefore, does not strike one as being the causative agent here.

Finally, the acinar tissue of the pancreas should be mentioned. The presence of adequate duodenal pancreatic ferments, together with normal stool findings, seems to absolve the acini. Perhaps these tests are too gross for this type of disease. Nevertheless, even the technic of Bauman and Whipple[13] proved more helpful in obstructive pancreatic disease than in the sclerosing type characteristic of hemochromatosis. The evidence against the pancreatic acini is only circumstantial, to be sure, and yet one has the feeling that the pancreas is more guilty than the liver in this case.

Most studies of the pancreas in fat metabolism mention fat accumulations in the liver. It should be pointed out that the remaining liver parenchyma and its regenerates here are not fatty. This is true despite the lipemia and probably pancreatic insufficiency — a combination that might be considered ideal for the production of fatty liver. Here, as also in "idiopathic hyperlipemia," the liver is kept free from fat accumulations in an "environment of plenty," so to speak. One cannot, therefore, identify the specific reason for this lipemia with certainty.

At present, more than two years since his diabetes was first discovered, and despite a gradually increasing lipemia, the patient works every day. The fasting urine remains sugar free on 50 units of protamine zinc insulin. But the underlying lesion apparently continues unabated, for a dermal scar at the site of the liver biopsy has developed the gunmetal pigmentation often associated with hemochromatosis.

SUMMARY

A case of lipemia associated with hemochromatosis is reported. Skin biopsy, liver needle sections

and bone-marrow aspirations showed hemosiderin deposits. Probable factors in this lipemia are suggested, though none can be proved.

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THE MEDICAL EXAMINER AND THE PRACTICING PHYSICIAN*

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IN THE Commonwealth of Massachusetts, medical examiners and associate medical examiners are county officers appointed for a term of seven years for the purpose of investigating certain classes of deaths. Chapter 38 of the *General Laws* of the Commonwealth (as amended by Chapter 632 of *Acts and Resolves* of 1945) states:

> When any person in the Commonwealth is supposed to have died by violence or by the action of chemical, thermal or electrical agents or following abortion, or from diseases resulting from injury or infection relating to occupation, or suddenly when not disabled by recognizable disease, or when any person is found dead, it shall be the duty of any person having knowledge of such death to notify the medical examiner of the district of the county wherein the body lies of the known facts concerning the time, place, manner, circumstances, and cause of such death. A physician who, having knowledge of such a death, fails to notify the medical examiner shall be punished by a fine of not more than one hundred dollars.

In brief, the six categories of deaths to be investigated are violent; chemical, thermal or electrical; deaths resulting from induced abortion; occupational deaths resulting from injury or infection; sudden deaths in the absence of recognizable disease; and persons found dead.

On receipt of notification of a death, there are three courses open to the medical examiner. He may decline jurisdiction over the case, referring it to the attending physician or to a board-of-health physician (if there is one) for certification regarding the cause of death. He may assume jurisdiction, scrutinize available information, make a *view* of the body (external examination) and certify the cause of death himself. Or he may view the body and then perform an autopsy or cause one to be performed.

When may a medical examiner decline jurisdiction? He may decline when, after ascertaining the available facts, he is satisfied that the death was caused by disease not related to the six categories outlined above.

Who shall certify a death when the medical examiner declines? The attending physician shall certify if he is available and if he attended the decedent at least twice, the last visit being within two weeks before death. If the physician who attended the decedent during his terminal illness is not available or if there has been no attending physician, a board-of-health physician may certify. Thus, board-of-health physicians (in areas where they are appointed) certify the deaths of those disabled by recognized disease not related to the six categories of medical-examiner cases when the attending physician has not seen the decedent within two weeks or when he is absent. Either the mother's physician or a board-of-health physician may certify stillbirths if there has been obstetric or general medical care prior to the birth, and if there is no question of violence, illegitimacy or birth injury.

What are the rules requiring that cases be reported to the medical examiner? The rules of practice vary somewhat among the medical-examiner districts and are evolved usually by collaboration between the medical examiner and the local board of health. In most districts the following cases should be reported:

Any death thought to fall into one of the six categories established by the *General Laws*.

Any hospital death within twenty-four hours of admission.

Any hospital death when the decedent was unconscious on admission and remained so.

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Any death pronounced by a physician other than the attending physician.

Any death when the patient was not attended by a physician within two weeks.

All such cases should be reported, but many will be declined at the time of reporting, and others after a preliminary investigation. For example, a man who collapsed at home or in his office and died fifteen minutes after hospital admission may be found to have been treated by the referring physician for a myocardial infarction five days previously. In another case in which a woman dies within twenty-four hours of admission to a hospital in coma the medical examiner may infer from the excessive obesity of the patient, from a positive history of hypertension and from a negative history of trauma that death was due to natural causes. Such cases may be declined by the medical examiner if he is satisfied that there are no reasonable grounds for suspecting that the death was caused or contributed to by physical or chemical injury or occupation.

What is the limit of time between injury and death within which a death must be reported to the medical examiner? There are no limits if the reporting physician believes that the injury caused or contributed to the death. Although the passage of time between injury and death may eliminate criminal responsibility, prevent tort action (damage suit) and make insurance claims contestable, intricacies of law, as when the damage was recognized, make it imperative that the medical examiner make an official record of the circumstances. Where there is not a clearly demonstrable relation between injury and death, the medical examiner may apply the British rule and decline such cases having a time interval in excess of a year and a day.

When may a medical examiner perform an autopsy? According to Chapter 38 of the *General Laws*, as amended:

> If on view of the dead body and after personal inquiry into the cause and manner of death, the medical examiner considers a further examination necessary in the public interest . . . [he] on his own authority may . . . make or cause to be made in his presence, an autopsy on the aforesaid body.

In other words, medical examiners are required to perform an autopsy only if it appears to be necessary in the public interest. A death that is a police matter is apt to require post-mortem examination, either to exonerate a suspect or to substantiate a suspicion. In general, cases likely to reach the criminal courts require autopsy. A death thought to be the result of virulent contagious disease may well require post-mortem confirmation because of the possible hazard to public health. A death related to occupation in industry, as a result of either injury or infection, may require autopsy in the public interest if others in that industry are exposed to the same hazard. Post-mortem examination of the body of an unknown person found dead may be desirable first, to determine the cause of death and, second, to provide information about the presence of chronic disease, the nature of past surgical procedures, old injuries, and any other anatomic fact that might add to the description of the unknown.

When the circumstances have established that an autopsy may reasonably be required in the public interest, the second criterion should be met—namely, that post-mortem dissection is *necessary* to establish either cause or manner of death. The body of a man who was seen by reliable witnesses to slip, fall and strike his head and who subsequently died in a hospital with x-ray films showing extensive fractures of the skull does not ordinarily require autopsy. If, on the other hand, a man were found unconscious on the street and subsequently died in a hospital without regaining consciousness and with signs of severe head trauma it would be necessary to perform a postmortem examination to determine to the fullest extent the nature of the injuries. Thus, it is in the public interest to establish whether there was one or multiple impacts; the size and the shape of the object that produced injury; and the presence or absence of disease or intoxication that may have predisposed the deceased to accident or assault. In essence, then, an official autopsy is necessary in cases in which precise detail regarding cause is of value, such as those destined for criminal courts, those in which the manner of death may be ascertained in part or in entirety by determination of the nature of injuries and those in which information contributing to identification may be acquired.

Under certain circumstances a medical examiner is required to perform an autopsy when so instructed:

> [The medical examiner] if he be so requested by the district attorney or the attorney general, shall make or cause to be made in his presence, an autopsy on the aforesaid body. . . . Upon written order of the district attorney of the district where the body lies, or of the attorney general, a medical examiner shall also make, or cause to be made in his presence, an autopsy. . . of any dead body within this county.

In simpler wording, on request — verbal or written — of either the attorney general or the district attorney, a medical examiner is required to perform an autopsy.

It should now be clear that a medical examiner does not act according to whim. He declines jurisdiction, or accepts and views a case, or performs an autopsy according to certain rules, which are derived from the *General Laws* of the Commonwealth. The most important function of the medical examiner is to protect the public by the acquisition of accurate medical evidence in deaths known or suspected to have resulted from criminal action.

An almost equally important function is to assist in the protection of public health from epidemic disease and industrial hazards. An incidental function is to investigate and furnish official records of deaths resulting from trauma of any sort, thereby protecting the rights of employee and employer, policyholder and insurer, civil claimant and defendant in all claims and suits for damages.

In metropolitan areas friction sometimes exists between the resident staffs of the hospitals and the medical examiner's office. It is apparently the firm belief of many of the younger physicians that the medical examiner acts in an ignorant, capricious and indifferent manner, especially with respect to performing autopsies. It is hoped that the exposition of the duties and limitations of power of the office presented above may eliminate this impression. Such critics, if they grant that the medical examiner must certify the cause and manner of death of certain cases without the right to autopsy, complain that bodies are removed from the hospitals by the medical examiner merely for viewing at a mortuary or undertaking establishment without allowing medical attendants the opportunity to seek permission for post-mortem examination by the hospital pathologist. The major cause for removal of bodies solely for view is the inadequacy of information furnished by the hospital to the medical examiner. Frequently, when the reporting hospital is unavoidably limited in information the medical examiner's office must seek out police reports or the records of other hospitals, or perhaps initiate a police investigation. In the interim, after enduring delays due to locating witnesses and reaching hospital record rooms (open from 9 in the morning to 5 in the afternoon except Saturday afternoon and Sunday), the family has selected an undertaker, and the medical examiner has no right to delay the funeral further to enable the attending physicians to have additional time to solicit permission for autopsy. Sometimes the co-ordination between the administrative and professional staffs of a given hospital is at fault. A case may be declined by the medical examiner and the administration of the hospital notified, but no word is sent to the professional staff that the way is open to request permission.

Often there are limits to the physical capacity of the medical examiner to fulfill his prescribed duties. If during a twenty-four-hour period 10 medicolegal deaths are reported, with between 1 and 5 autopsies necessary in the public interest, it is obviously impossible to travel from place to place to view bodies under trying circumstances. There is, however, a solution to the difficulty. If each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital, more cases would be available for hospital autopsy. No medical examiner, pathologist or general practitioner will deny that autopsy is desirable for the common good.

MEDICAL PROGRESS

BAL*

RAYMOND V. RANDALL, M.D., AND ALBERT O. SEELER, M.D.†

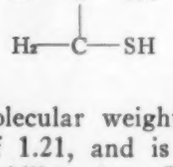
BOSTON

THE discovery of BAL (2,3–dimercaptopropanol) by Peters and his co-workers[1] in England was the result of an intensive search for a substance that would be effective in treating severe burns caused by contact with certain arsenical war gases such as lewisite. The name BAL is an abbreviation of "British Anti-Lewisite," a term applied to this substance after it had proved to be effective against lewisite. It was soon found that this compound was of value not only in treating the local effects of arsenical war gases but also in combating the systemic disturbances following their absorption. Moreover, BAL proved to be effective in the treatment of toxic reaction caused by arsenical drugs used in the therapy of syphilis. Further investigation showed that the substance was of value in the treatment of poisonings from a number of other metals.

The studies on BAL and related compounds have not only led to the development of a valuable therapeutic agent but also contributed to an understanding of the mode of action of various metals.

CHEMISTRY AND PROPERTIES[2–4]

The chemical name for BAL is 2,3–dimercaptopropanol. It contains two thiol groups (also known as sulfhydryl [–SH] groups) and consequently 2,3–dithiopropanol is a commonly used synonym. Its structural formula is:



BAL has a molecular weight of 124.2 and a specific gravity of 1.21, and is an oily, colorless liquid with a skunklike odor. In common with a number of closely related dithiols, the compound is a sluggish, nonautoxidizable, oxidation-reduction system, easily oxidized in the presence of a number of catalysts, especially copper and iron porphyrins. BAL reacts with a number of metals to form BAL-metal complexes. Colored complexes are formed with iron, lead, bismuth, tin, copper, cobalt, nickel, antimony and selenium. Zinc, cadmium and mercury combine with BAL to give white precipitates, and magnesium and manganese form colorless, soluble complexes. BAL instantaneously converts methemoglobin to oxyhemoglobin in the presence of oxygen.

BAL is soluble in water to the extent of 6 per cent (weight/volume). Because it is readily oxidized, aqueous solutions are unstable and must be prepared immediately before use. The compound is relatively stable in peanut oil, but soluble in this vehicle only to the extent of 5 per cent (weight/volume). However, when it is mixed with benzyl benzoate in the ratio of 1 part of BAL to 2 parts of benzyl benzoate it is miscible with peanut oil in all proportions. Such preparations are homogenous but become cloudy at icebox temperatures. This cloudiness readily disappears when the preparation is warmed to room temperature. Commercial preparations of BAL contain 10 per cent BAL and 20 per cent benzyl benzoate (weight/volume) in peanut oil and are suitable for intramuscular use only. Sterilization of such preparations by autoclaving at 120°C. for twenty minutes may cause the loss of as much as 15 per cent of the available sulfhydryl groups by oxidation. If, however, these preparations are placed under nitrogen they may be autoclaved without significant decomposition.

MODE OF ACTION OF HEAVY METALS AND BAL

During the past twenty-five years, the concept has arisen that heavy metals owe their toxicity, at least in large part, to their ability to combine with sulfhydryl groups of the protein fractions of enzymes. Studies that ultimately led to this concept and to the development of BAL began in 1923 when Voegtlin, Dyer and Leonard[5] showed that glutathione, as well as other monothiols (substances containing one thiol or sulfhydryl group), could counteract the toxic action of arsenoxides on trypanosomes both in vitro and in vivo. They further showed that glutathione delayed the onset of symptoms and death in rats given a lethal dose of arsenoxide. On the basis of these findings, they postulated that arsenoxide could be regarded as a specific poison affecting the sulfhydryl groups of some essential protoplasmic constituent. The addition of the monothiols presumably supplied extra sulfhydryl groups, which united with and thereby counteracted the toxicity of the arsenic. The au-

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thors also assumed that the union between the arsenic and the added sulfhydryl groups was not stable — otherwise glutathione would have prevented rather than merely delayed death in rats given lethal doses of arsenic. Further evidence of the relation of sulfhydryl groups to the toxicity of arsenic was the observation of Walker[6] in 1928 that *Colpidium colpoda*, a unicellular organism, could be temporarily revived after arsenic poisoning by the addition of sodium thioglycollate.

Similarity in the mode of action of arsenic, bismuth and mercury compounds was demonstrated in 1939 by Eagle,[7] who showed that various sulfhydryl-containing substances abolished the antispirochetal action in vitro of bismuth and mercury as well as of arsenic. He found that thiamine chloride and methionine, which contain sulfide (-S-) rather than sulfhydryl (-SH) groups did not have a similar inhibitory effect on these heavy metals

Studies on proteins and enzyme systems have also been carried out in an attempt to discover the mode of action of arsenic. Szent-Györgyi,[8] in 1930, showed that arsenic strongly inhibited the respiration of minced liver tissue. Voegtlin, Rosenthal and Johnson[9] found that glutathione added to rat tissue slices prevented the reduction in oxygen consumption caused by arsenic alone. These findings also suggested that sulfhydryl groups were intimately concerned with tissue respiration, and that the action of arsenic upon living tissue was primarily through the tissue's sulfhydryl compounds. Further evidence in support of these views was forthcoming in 1932, when Rosenthal[10] showed that although arsenic combined with proteins containing sulfhydryl groups, it did not combine with proteins in the absence of these groups.

In the course of studies on arsenical war gases, Peters, Sinclair and Thompson[11] found the enzyme pyruvate oxidase to be sensitive to small concentrations of arsenic or lewisite. Since none of the coenzymes known to be concerned with the pyruvate oxidase system were sensitive to lewisite, it was concluded that the point of attack of arsenic was upon a protein component of the enzyme system. It was soon demonstrated that a protein containing sulfhydryl groups was essential for the function of pyruvate oxidase and that blockage of these groups would inactivate the enzyme.[12] These findings indicated that the toxic action of arsenic was due, not to some nonspecific denaturant or coagulant effect upon cellular constituents, but to enzyme inhibition.

In contrast to the work mentioned above, wherein it had been found that monothiols afforded protection against various arsenic compounds, Sinclair (as quoted by Peters et al.[1]) found that monothiols, even when present in large excess, failed to protect pyruvate oxidase from the toxic action of lewisite. It, therefore, seemed important to reinvestigate the nature of the union between arsenic and protein sulfhydryl groups. Since it was impossible to obtain an arsenic-sensitive enzyme, such as pyruvate oxidase, in a purified state, Stocken and Thompson[13] studied kerateine, a derived protein containing many sulfhydryl groups. They found that at least 75 per cent of the arsenic in the lewisite-protein complex was in combination with two sulfhydryl groups. Additional findings made it seem probable that the arsenic had combined with two sulfhydryl groups closely placed on the same protein molecule to form a ring. On physiochemical grounds it was predicted that

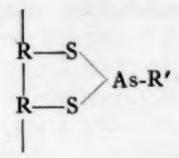

FIGURE 1. *Ring Structure.*

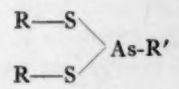

FIGURE 2. *Open-Chain Structure.*

a ring compound (Fig. 1) would be more stable than an open-chain structure formed by the union of arsenic with two monothiol molecules (Fig. 2). On the basis of this reasoning, it appeared that a substance capable of competing successfully with tissue proteins for arsenic must also be capable of forming a ring compound as stable as, and preferably more stable than, that formed between arsenic and the proteins. Supporting this view was the work cited above[5-7] showing that monothiols delayed but did

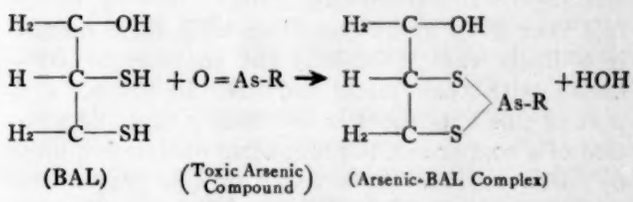

FIGURE 3. *Reaction Between Arsenic and BAL.*

not always prevent the death of animals poisoned with arsenic.

Stocken and Thompson[14] decided to experiment with various dithiols because they believed that these compounds with their two sulfhydryl groups might be capable of forming stable cyclic combinations with arsenic. Numerous dithiols were tested, some with as many as 12 carbon atoms between the two sulfhydryl groups, and a number were found to react with arsenic to form a stable ring structure. However, not all the latter compounds were satisfactory on pharmacologic grounds, and it was only after extensive animal studies that BAL was selected as the most promising compound.

It now seems clear that the antidotal action of BAL lies in its ability to unite with arsenic to form a relatively stable cyclic compound and thus to compete successfully with the sulfhydryl groups of tissue proteins for arsenic. This action is both prophylactic and therapeutic, because BAL can unite with arsenic before it enters into combination with the tissues (Fig. 3) as well as wrest arsenic away from the tissues (Fig. 4).

Pharmacology

Action on Enzymes

In an attempt to arrive at an understanding of the toxicity of BAL, Webb and van Heyningen[15] studied its action on a large number of enzyme systems. They found seven enzymes to be strongly inhibited by BAL: polyphenol oxidase, carbonic anhydrase, catalase, peroxidase, aldehyde mutase, phosphorylase and glyoxalase. Of these, four are known to be metal-containing enzymes: polyphenol oxidase (copper), carbonic anhydrase (zinc), catalase (iron), and peroxidase (iron). In view of the fact that BAL forms complexes with these metals[3] it is likely that it inhibits the enzymes by combining with their metal radicals. In further support of this hypothesis is the finding that the addition of a copper salt to polyphenol oxidase inhibited by BAL restores the activity of this copper-containing enzyme. Cytochrome oxidase is the only metal-containing enzyme that was examined and found not to be inhibited by BAL. This was thought to be due to a rapid oxidation and inactivation of BAL when it comes in contact with this enzyme. No explanation is offered for the inhibition of aldehyde mutase and phosphorylase, although it is pointed out that these, too, may be metallic enzymes. It is believed that glyoxylase, which does not contain a metal but does contain glutathione (a monothiol), is inhibited by BAL, because the BAL can compete successfully with the monothiol for a position in the enzyme structure.

Barron et al.[16] found that BAL decreased the respiration of tissue slices and inhibited cytochrome C and succinoxidase. They also noted that BAL destroyed the activity of insulin by reduction of its –S–S– linkages.

Absorption, Metabolism and Excretion[17-21]

Studies with radioactive BAL (BAL containing radioactive sulfur) have shown that it is slowly absorbed through the skin but rapidly dispersed once it penetrates the cutaneous barrier. Radioactive BAL given intramuscularly has disappeared rapidly from the site of injection, with no radioactivity remaining at the site after six hours. Within five minutes after instillation into the conjunctival sac of the rabbit, BAL has been recovered from the aqueous of the anterior chamber.

Experiments with rabbits given intramuscular injections of radioactive BAL have shown that 80 per cent of the injected BAL entered the circulation and was distributed throughout the body within an hour of injection. A fairly uniform blood level was maintained for two hours. This level was halved by the third hour, and fell to a third of the original value by the seventh hour. Aside from somewhat higher concentrations in the kidney and intestine, BAL was diffusely distributed throughout the body.

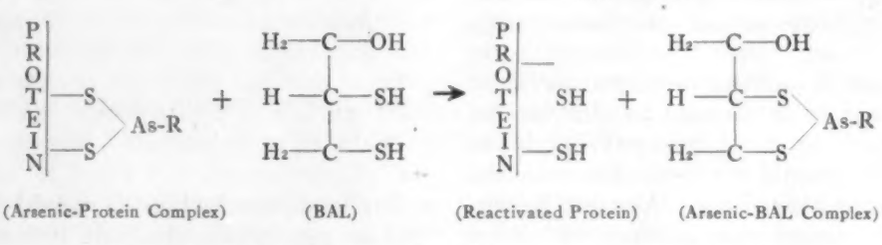

FIGURE 4. *BAL Reactivation of an Arsenic-Poisoned Tissue Protein.*

Only minute amounts of BAL have been found to be excreted by the respiratory tract although its skunklike odor may be detected in the expired air. Studies have shown that the major portion of absorbed BAL is rapidly metabolized and excreted in the urine. After single injections of radioactive BAL, 45 per cent of the total radioactivity could be recovered from the urine within six hours, and 81 per cent within twenty-four hours. Only a small proportion of the radioactive substances recoverable from the urine was in the form of unchanged BAL.

Action on Animals

In general, the signs and symptoms of BAL toxicity are ushered in by an initial period of apathy accompanied by lacrimation, blepharospasm and conjunctival edema. With increasing dosage, one finds in addition to the above: muscle tremors of gradually increasing intensity; inco-ordination; ataxia, especially of the hind limbs; dyspnea; and finally generalized clonic convulsions, coma and death. Only an occasional animal recovers once convulsions have begun. An early transient rise in

blood pressure is common, but this soon gives way to vascular collapse.[22, 23]

Undiluted BAL applied directly to the skin and mucous membranes causes localized redness, edema and capillary injury.[23, 24]

Electroencephalograms taken during BAL-induced convulsions in rabbits have revealed that they are not cortical in origin. Studies following transection of the thoracic cord further showed that the convulsions do not arise in the cord. The exact site of origin has not been established. Sodium pentobarbital controlled these convulsions, but death from vascular collapse usually occurred.[22]

In moderate doses, BAL is a respiratory stimulant. Large doses stimulate respiration initially, but severe depression of the respiratory center follows.[22, 23]

BAL causes an initial arteriolar constriction resulting in a rise in blood pressure. This effect is not mediated through the central nervous system, but is the result of a direct action upon the vessel walls. Subsequently, BAL may cause extensive capillary damage, which can lead to irreversible shock.[25, 26]

In dogs, an intramuscular, lethal dose of BAL (100 mg. per kilogram of body weight) has produced early hyperglycemia with glycosuria and subsequent preterminal hypoglycemia. Convulsions occurring in these animals were not hypoglycemic because they began while the blood sugar was still elevated. Histologic examination of the liver failed to reveal any evidence of hepatic-cell damage.[22] However, fatty degeneration and occasional necrosis have been found in the livers of dogs given daily intramuscular doses of 15 to 30 mg. per kilogram of body weight for four days.[27] The possibility that the clinical use of BAL might be contraindicated in some cases of hepatic damage has been raised by the finding that animals with livers damaged by carbon tetrachloride showed toxic signs after doses of BAL that were ordinarily well tolerated.[28] However, BAL has been used in a number of patients with so-called postarsenical hepatitis, and there is no mention of extraordinarily toxic manifestations occurring in these persons.

Although the anticoagulant effect of BAL in vitro is pronounced, doubling the prothrombin time of human plasma, it has not been reported to produce hemorrhagic tendencies in vivo. Fantl and Nance[29] found that rabbits given BAL intramuscularly showed no changes in prothrombin time or coagulation time.

In general, histologic studies of animals receiving both single and repeated doses of BAL have failed to reveal conspicuous morphologic changes except in those dying from acutely lethal doses. Such animals show pulmonary hemorrhages and edema, which are probably the results of the marked vascular action of BAL. Isolated instances of thickening of alveolar walls and renal tubular degeneration have been seen, but it is impossible to correlate these rare findings with the administration of BAL.[23] As noted above, liver damage has been observed to follow large doses.

Action on Man

All clinicians who have written about the therapeutic uses of BAL warn of the undesirable side effects that may occur. Eagle and Magnuson[30] have reported the incidence of toxic manifestations following the intramuscular administration of BAL to 60 normal subjects and 61 patients with arsenical poisoning. At a dose level of 2.5 mg. per kilogram of body weight, less than 1 per cent of injections were followed by mild toxic signs and symptoms. At a level of 4 mg. per kilogram, mild to moderate reactions were noted in about 15 per cent of cases, and at a level of 5 mg., 50 to 60 per cent had reactions. Localized pain at the site of injection was not uncommon, but it was no more severe than that seen after the intramuscular administration of a number of other therapeutic agents. The usual toxic manifestations were nausea, vomiting, headache, burning sensations of the mouth and eyes, lacrimation, profuse salivation, rhinorrhea, muscular aches, tingling of the extremities, sweating of the forehead and hands, pain in the teeth, a sense of constriction in the chest, anxiety and general agitation. Transient elevation of blood pressure was common. The symptoms began about ten to twenty minutes after the injections, reached a maximum in twenty to thirty minutes, and disappeared within fifty to ninety minutes. These findings are in accord with those of Modell et al.,[31] who, in addition, observed that single doses of 8 mg. per kilogram of body weight almost invariably produced marked symptomatology. They also found that doses of 5 mg. per kilogram could be repeated every three hours for twenty-four hours without significant cumulative effects.

Woody and Kometani[32] reported the case of a child who received two overdoses of BAL of 25 mg. per kilogram each. Thirty minutes after the first overdose the child developed anorexia, vomiting and restlessness, all subsiding in an hour. Ten minutes after the second overdose (given three hours later) examination showed cutaneous flushing, mild hyperpyrexia, tachycardia, hypertension, a generalized convulsion lasting for three minutes and coma and stupor lasting for an hour. After the coma the child appeared to be normal, and recovery was uneventful.

Localized abscesses at the site of injection occur occasionally.[30] They seem to occur most frequently in cases of arsenical dermatitis in which the intramuscular needles have passed through infected tissues, and, therefore, are probably the result of secondary infection rather than a direct action of BAL upon the tissues.

Application to the skin can cause varying degrees of localized reactions ranging from mild erythema

to severe whealing and capillary damage.[19] Sulzberger[33] was able to create skin sensitization with repeated applications of a 5 per cent BAL ointment to normal skin. Sixteen of 88 human subjects (19 per cent) developed localized reactions varying from faint erythema with pinhead-sized, papulo-urticarial lesions to marked erythema with confluent urticarial and papular lesions lasting up to five days. These relatively persistent lesions should be distinguished from the erythema and whealing frequently noted after topical application of BAL, which disappear in fifteen minutes to two hours. When applied to skin previously damaged by mustard gas, BAL caused a definite dermatitis in 35 out of 53 subjects (66 per cent).

Epinephrine has been used successfully to alleviate the undesirable side effects of BAL: 0.6 of 1 cc. of 1:1000 epinephrine hydrochloride solution gave rapid and complete relief. Oral or parenteral administration of 25 mg. of ephedrine sulfate half an hour before the administration of BAL prevented the onset of symptoms.[34]

Compounds Related to BAL

Although many compounds related to BAL have been studied, only two are of particular interest — namely, the ethyl ether of BAL and BAL glucoside.

The ethyl ether of BAL is more toxic than BAL. Whereas the initial toxic manifestations of this compound are similar to those produced by BAL, death, when it occurs, is not acute but is almost invariably delayed for days or weeks. Even doses forty times greater than those necessary to produce mild symptoms do not kill immediately. In spite of its comparatively great toxicity the ethyl ether of BAL is of interest because it is more effective than BAL in the treatment of arsine poisoning in animal experiments.[24, 35]

BAL glucoside (BAL-intrav) is much less toxic than BAL and has the advantage of being freely water soluble. Doses as large as 100 mg. per kilogram of body weight have been given intravenously to man without apparent ill effects, whereas BAL itself may produce symptoms when given intramuscularly in doses of 4 mg. per kilogram. Unfortunately, there are not sufficient data to permit a quantitative comparison of the therapeutic activity of BAL glucoside with BAL, but the limited information available suggests that the former has a more satisfactory therapeutic index than the latter.[36-38]

BAL in Specific Poisonings

Although the immediate interest at the time BAL was developed was the treatment of arsenical wargas poisoning, it soon became apparent that the compound was of value in the therapy of arsenical poisoning in general. Investigation of its value in other heavy-metal poisonings indicated that BAL could not be used indiscriminately in the treatment of all because in some cases it not only was valueless but also actually appeared to enhance the toxicity of a metal. The concluding section of this progress report will be devoted to a discussion of the role of BAL in the treatment of specific metal poisonings, and mention will also be made of the effects of BAL on the action of alloxan and phenylthiourea.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 34521

PRESENTATION OF CASE

A fifty-five-year-old man entered the hospital because of abdominal cramps and distention.

Three weeks before admission the patient noted the gradual onset of an illness characterized by abdominal swelling and diffuse abdominal cramps. He felt bloated constantly and, in addition, had spasmodic, doubling, abdominal pains, which lasted about a minute and which he could not localize. There was a slight reduction in the number of bowel movements but no change in the character of the stools was noticed. There was no obstipation or passage of bloody, tarry or clay-colored stools. Though the patient's appetite remained good, he ate infrequently because his capacity for food was greatly reduced. A normal-sized meal nauseated him, but he never vomited. The urine was brown as it had been for several years. The legs and ankles became moderately swollen.

The patient had had diabetes for five years. He had been taking 10 units of protamine insulin daily until admission. For three years he had been subject to anginal attacks precipitated by exercise and relieved by nitroglycerin. There had been several episodes of ankle edema, orthopnea and nocturnal dyspnea. He had felt weak and tired since an attack of "virus pneumonia" five months before admission. He thought he had lost weight since that time but did not know how much. About four years before admission he had been jaundiced and felt weakness and malaise for three weeks. There had never been any previous episodes of abdominal symptoms.

The patient's father had died of diabetes, and a brother had the disease.

Physical examination showed a patient who appeared chronically ill and in moderate distress. The skin of the extremities and back had a dusky, cyanotic tinge. The tongue was thickly coated, and the breath fetid. The abdomen was distended, tympanitic and nontender. There were shifting dullness and a fluid wave. No organs or masses were palpable. There was a soft, apical, systolic murmur. The lungs were clear. There was moderate pitting edema extending halfway up the leg, and slight pressural edema.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 4,400,000, with a hemoglobin of 16 gm., and a white-cell count of 8000, with 70 per cent neutrophils. The urine had a specific gravity of 1.012. The sediment was normal, and a test for bile was negative. There was a green sugar reaction. The stools were brown, formed and guaiac negative. The blood chemical values on admission were as follows: sugar 200 mg., nonprotein nitrogen 20 mg., and protein 5.8 gm. per 100 cc.; bilirubin 0.7 mg. per 100 cc. direct, 1.1 mg. indirect; and carbon dioxide 31 milliequiv. and chloride 88 milliequiv. per liter. X-ray studies of the chest and abdomen showed both leaves of the diaphragm to be high, with haziness in the costophrenic sinuses. There was marked gaseous distention of the bowel, which could not be localized but was thought to affect both colon and small bowel. The peritoneal markings were not clear, indicating the presence of the fluid.

In the hospital the patient had a daily temperature between 100 and 102°F. A barium enema on the second hospital day showed delay of retrograde flow in the region of the splenic flexure, though barium passed into the dilated gas-filled and fluid-filled transverse colon. No definite lesion could be made out. The small intestine was also dilated. The urine reaction remained green on 10 units of regular insulin daily. The patient had a shaking chill on the third hospital day.

An exploratory laparotomy was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JAMES H. TOWNSEND: May we see the x-ray films?

These x-ray films are very impressive. We were not told about all this tubing, but there it is.

DR. STANLEY M. WYMAN: We have only a few films from the original examination. Some of them were lost, apparently. The heart is definitely enlarged, chiefly toward the left, probably in the region of the left ventricle. The aorta is tortuous, and there is some calcification. There appears to be a small quantity of fluid in the left costophrenic angle and possibly on the right also. The lung fields reveal no definite intrinsic disease. The appearance of the chest is consistent with hypertensive arteriosclerotic heart disease, with probable fluid in both pleural spaces. This film of the abdomen with a Miller–Abbott tube in place was taken the day following the barium enema examination. The barium enema was done with the Miller–Abbott tube in place and quite a way down, as you see from the spot films. The patient was not prepared, and the examination, I gather from the record, was unsatisfactory. The fluoroscopist, in running the barium into the descending colon, arrived at the splenic flexure, where he had difficulty in forcing the barium farther. He took a number of spot films, which show barium passing into the distal transverse colon, where there is considerable fluid and retained material. The spot films of the area reveal no evidence of intrinsic filling defect, no definite kinks and no definite constriction by adhesions. I can say only from the films available that there was delay in the barium column at this point without a definite organic lesion. To go back to the plain film of the abdomen, there is a haziness that suggests fluid in the abdomen. This has to be taken with skepticism because this is a grid film.

DR. TOWNSEND: From the data given I am sure that I shall be unable to make a precise diagnosis. However, there are certain possibilities that I can discuss.

To summarize the positive features, this fifty-five-year-old man, who was known to have had diabetes for five years, had an episode described as jaundice, which I think must always be taken with reservation. Four years before he had had what was called angina. For three years he had had a number of episodes of ankle edema, orthopnea and nocturnal dyspnea. Five months before admission he had what was called "virus pneumonia," and which easily could have been something else, perhaps pulmonary embolism or some other circulatory disturbance in the chest. He was brought to the hospital by an illness of three weeks' duration, characterized by abdominal cramps and swelling of the abdomen and of the ankles, and while in the hospital he had fever.

The physical examination showed a dusky color, apparently cyanosis, although there may have been something else about the color, a coated tongue, definite ascites and fever. From the laboratory evidence there was mild jaundice, elevated plasma bilirubin, both direct and indirect, a slight reduction in serum protein, with a slight alkalosis and slight hypocalcemia, possibly associated with diet. I assume that since this man had cardiac failure he may well have been on a diet low in sodium chloride, which may have a bearing on the chloride of 88 milliequiv. per liter. It is noteworthy that he did not have anemia and that the nonprotein nitrogen was normal. The blood sugar was high enough to prove the diabetes but not strikingly high. He did not have bile demonstrated in the urine. He apparently had normal amounts of bile in the stools. X-ray films suggest fluid in the pleural cavities and in the abdomen and gas-filled loops of bowel, which the x-ray people could not interpret entirely. They could not tell whether the whole intestine was dilated — paralytic ileus — or whether examination showed an obstructing lesion.

What are some of the possibilities? If we try to put them all together and put them on a cardiac basis, there seems little reason to doubt that this fifty-five-year-old man with diabetes had coronary-artery disease manifested by angina pectoris and symptoms of congestive failure. He also had a somewhat enlarged heart, and we wonder if the blood pressure had not been higher in the past than at present. We have no electrocardiographic evidence. I think we might say that he undoubtedly had coronary-artery disease and that he probably had some congestive failure. Could the cardiac condition have led to abdominal symptoms? Could he have had a mesenteric thrombosis or other thrombosis in the abdominal cavity? Yet if he had real mesenteric embolus, such as might come from thrombosis within the heart, one would hardly expect him to live three weeks. The episode would have been much more critical, and he would have died or been in serious trouble within a few hours as a rule. Is there anything about the cardiac condition that might lead to jaundice and ascites? Yes. Jaundice is not common in cardiac failure, although it may occur. Ascites may occur in most types of heart failure associated with right-sided heart failure, such as that seen with adhesive pericarditis or tricuspid lesions or with long-standing, definite, congestive failure, in which the nutmeg type of liver and, possibly, slight jaundice occur. However, this does not sound like that sort of history.

Are there any abdominal conditions that are part and parcel of the diabetes? There are at least three types of abdominal conditions that can produce abdominal symptoms and have diabetes as a feature. One is chronic pancreatitis, with enough destruction of islet tissue to produce diabetes, and I think it is possible that this patient could have had chronic recurrent pancreatitis. Jaundice and ascites can occur with it. This is a possibility, but I can see no way to prove it. The second abdominal condition associated with diabetes is a special form of liver cirrhosis, pigment cirrhosis. Hemochroma-

tosis is associated with diabetes, usually from pancreatic fibrosis from pigment. This is seldom associated with jaundice, but I recall a case given to me a year or so ago in which four years before death the patient showed evidence of cirrhosis, including jaundice and ascites, and at that time on biopsy showed early Laennec's cirrhosis. Four years later, at the time of death from liver failure, there were extensive pigment deposits of the type called hemochromatosis. That is a possibility, but we have very little evidence, and I do not see how one can make the diagnosis.

Another possibility is cholesterol disease. We are not given the value of the blood cholesterol, but there is a condition of hypercholesterolemia, which can be associated with deposits of cholesterol with fibrosis in the pancreas sufficient to cause diabetes. This also may be associated with enlarged liver and occasionally with jaundice. However, I doubt very much that it would lead to ascites; at least, I have never seen it. It can also be associated with coronary-artery disease and frequently terminates with coronary thrombosis.

What other possibilities should we consider? Ordinary liver cirrhosis, I think, is entirely possible. We are not given the usual battery of liver tests. We are told nothing about the prothrombin time, the cephalin flocculation test or the phosphatase level. We do know that he had ascites and jaundice, and that combination is always suggestive of Laennec's cirrhosis of the liver.

What about gallstones? There is a history of an attack of jaundice, without pain, four years ago. This time there were pain and jaundice. However, there seems to be very little to suggest that the patient was troubled with cholelithiasis, and it would be rather hard to explain the terminal picture on that basis.

What about the possibility of carcinoma of the pancreas? I think the possibility of neoplasm in the last few weeks of his life cannot be excluded. It could have been in the pancreas (it can be almost anywhere). I doubt that there is sufficient evidence to make a diagnosis without looking inside, which we are going to do vicariously in a minute.

One other possibility: Could he have had a spontaneous thrombosis of some radicle of the portal vein? Such things do occur. They are very difficult to diagnose in life and very apt to be associated with crampy, abdominal pain of indefinite character. They can be rapidly followed by the development of ascites and edema and large enough to result in a large area of gangrene of the bowel, but this man would not have lived three weeks if that had occurred. Of all possibilities, I think this is the least likely. If I were to list my diagnoses, I would say, of course, diabetes mellitus, coronary-artery disease and, I think, intra-abdominal thrombosis, probably in the portal system, possibly in some way related to cirrhosis of the liver.

Dr. William Dock: I think these dusky legs make one think of hemochromatosis. That is an odd thing to have — cyanosis of the legs — without cyanosis of the lips, ears and fingers. With cyanosis of the back and legs it sounds as if he may have had an odd color, not merely diabetes with cyanosis, and it makes one suspicious. I think it is an important point. Patients with cirrhosis occasionally have bouts of fever and abdominal conditions unexplained by positive blood cultures or anything else. It may be that there was some intercurrent disease. However, I think this is a case in which terminal pylephlebitis ought to be thought of. I should think he might have had carcinoma in the tail of the pancreas. I would be inclined to guess that he had bronze diabetes and got into new troubles superimposed on his cirrhosis, so that he came in on the Surgical rather than the Medical Service.

Clinical Diagnoses

Large bowel obstruction,? carcinoma.
Diabetes mellitus.
Angina pectoris.

Dr. Townsend's Diagnoses

Diabetes mellitus.
Coronary-artery disease.
Cirrhosis of liver.
Intra-abdominal thrombosis.

Anatomical Diagnoses

Hemochromatosis, liver, pancreas, skin and lymph nodes.
Hepatoma, with extension into hepatic and portal veins.
Esophageal varices.
Ascites.
Splenomegaly.
Operations: exploratory laparotomy; bilateral femoral-vein ligation.
Thrombosis, left common femoral vein.
Hydrothorax.
Pulmonary congestion.
Chronic cholecystitis.

Pathological Discussion

Dr. John B. Stanbury: The patient did come in on the Surgical Service. It was thought when he was first seen that there was distention of the small bowel, and enough possibility of small-bowel obstruction to justify surgical exploration. That was done. No obstruction was found, but a nodular liver was observed from which a biopsy was taken. It showed a marked grade of cirrhosis with a great deal of hemosiderin deposit, and a diagnosis of hemochromatosis was made. The patient was then transferred to the Medical Service, and the prognosis seemed so hopeless that they were not very

much interested in doing any great battery of liver-function tests. The bromsulfalein test showed 40 per cent retention of the dye, and the thymol turbidity was 7 units.

DR. TRACY B. MALLORY: The patient died in two weeks. There was an episode suggesting pulmonary embolism following which the leg veins were ligated on both sides. From that time on there was constant seepage of fluid through the wounds where the veins had been ligated that could not be stopped. The peritoneal fluid evacuated at operation reaccumulated rapidly.

At autopsy we found that the liver weighed 3400 gm. and was very grossly nodular, with two types of nodules, quite sharply distinct in color. In cutting across the liver we found in the central portion a large tumor similar in appearance and color to one of the types of nodules. Also, many thrombi were found in both the hepatic and portal veins. So the diagnosis of primary hepatoma with invasion of the venous system of the liver was made. There was also a thrombotic occlusion of the portal vein behind the tumor thrombus. There was moderate involvement of the adrenal glands and pancreas, and the lymph nodes in the porta hepatis were deeply pigmented.

DR. TOWNSEND: Was any reason found for the rather sudden decline of the patient three weeks before entry?

DR. MALLORY: I imagine that represents the rapid progress of the hepatic carcinoma, which spread very quickly throughout the venous system of the liver.

DR. TOWNSEND: Do you often find hepatic carcinoma developing on the basis of hemochromatosis?

DR. MALLORY: I have the impression that I have seen it disproportionately often in hemochromatosis. I have seen figures saying that that is not so. Considering the rarity of hemochromatosis, I think a surprising number of patients die with hepatoma.

DR. JOHN B. QUINBY: What did the heart show?

DR. MALLORY: Mild atherosclerosis of the coronary arteries without narrowing and no infarction. The kidneys showed nothing remarkable.

CASE 34522*

PRESENTATION OF CASE

First admission. A fifty-one-year-old unmarried woman was admitted to the hospital because of severe epigastric pain. A diagnosis of gall-bladder disease was made. The symptoms subsided almost completely, and she was discharged on the fifth hospital day.

Fourth admission (four years later). In the interval the patient had two admissions for recurrent bouts of epigastric pain. During the last she underwent an exploratory laparotomy and appendectomy. The abdominal organs, including the gall bladder, were grossly normal. During this admission the patient was found to have an adenocarcinoma of the sigmoid colon, and a Mikulicz operation was subsequently done. She was discharged on the sixty-second hospital day.

Seventh admission (approximately twelve years later). In the interval the patient had been admitted on two separate occasions for a ventral hernia and for closure of the colostomy wound, the last admission being ten years before this one. At this time she was admitted because of increasing difficulty in swallowing and some weight loss. A roentgenogram showed findings consistent with carcinoma of the lower third of the esophagus. A biopsy showed epidermoid carcinoma, grade III. An esophagectomy and esophagogastrostomy were done, and the patient discharged on the forty-third hospital day.

Eighth admission (seven years later). In the interval the patient had been seen more or less regularly in the Tumor Clinic, and no evidence of recurrence of either the esophageal or the sigmoid cancer noted. Approximately one month before admission she began to have frequent attacks of sharp, stabbing pain in the right upper quadrant. This pain was severe and accompanied by nausea, vomiting and gaseous eructations. The pain radiated to the back but not into the shoulder. She denied any change in the stools or urine but admitted to being jaundiced with several of the attacks. The present episode had begun four days before admission.

Physical examination revealed a poorly nourished woman in no acute discomfort. The scleras and skin were questionably icteric. The lungs were clear. The abdomen was flat, and numerous dilated veins were seen coursing under the skin. There appeared to be a considerable amount of voluntary spasm. The right upper quadrant was tender to deep palpation, but neither liver nor gall bladder could be felt. The spleen was not palpable.

*Presented at a meeting of the New England Cancer Society held at the Massachusetts General Hospital.

Laboratory study revealed a serum van den Bergh of 1.8 mg. per 100 cc. direct and 2.0 mg. per 100 cc. indirect and an amylase of 116 units per 100 cc. The hemoglobin was 11 gm., and the white-cell count 6000. The specific gravity of the urine was 1.003, but examination was otherwise negative.

In the hospital the patient had another acute attack of pain, from which she was allowed to recover before operation. In the meantime she was given penicillin, streptomycin and three blood transfusions. On the twelfth hospital day a cholecystectomy and choledochostomy were done. One large and several small stones were found in the common duct, which was noted to be very large but soft. She convalesced well and was discharged on the tenth postoperative day. A cholangiogram done two days before discharge showed good filling of the biliary radicles, both intrahepatic and extrahepatic. There was some dilatation of the whole system, but the dye passed readily into the duodenum.

Final admission (two months later). In the interval the patient had been followed in the clinic and was very well when last seen, approximately six weeks before the present admission. She had continued to be up and about feeling well until two days before admission, when she noted the onset of anorexia and abdominal discomfort. On the following day she went to bed and had nausea and vomiting of blood of an unknown amount. She was also said to have passed blood by rectum. On the morning of the day of admission she was found unresponsive. It was also noted that the skin was yellowish. She was admitted in a state of coma.

Physical examination revealed a comatose, emaciated woman breathing heavily. The skin and conjunctivas showed jaundice. The lungs were clear. Abdominal and neurologic examinations were essentially negative. Rectal examination was negative.

The temperature was 98.6°F., the pulse 100, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Laboratory examination revealed a serum van den Bergh of 8.5 mg. per 100 cc. direct and over 12.5 mg. per 100 cc. indirect and a nonprotein nitrogen of 42 mg. per 100 cc. The carbon dioxide was 22 milliequiv. per liter, and the sugar 76 mg. per 100 cc. Determination of the prothrombin time was attempted, but the blood did not clot even after 120 seconds with a control of 16 seconds. The hemoglobin was 15 gm., and the white-cell count 9000, with 81 per cent neutrophils. The urine showed a ++ test for bile. A stool was guaiac negative.

On the following morning the patient's respirations were more rapid, and the jaundice deeper. Later that day respirations ceased, and she died.

Differential Diagnosis

Dr. Grantley W. Taylor: This is an extraordinary case. There are several points of considerable interest. First of all, this woman had a carcinoma of the colon at the age of fifty-five, which was cured apparently. At the age of sixty-seven she entered again with a carcinoma of the esophagus, which was an epidermoid, Grade III. This must represent one of the rare, very early cures of carcinoma of the esophagus because seven years later, when the gall bladder was operated on, I think it would have been remarked if she had shown any evidence of intra-abdominal extension or recurrence of carcinoma. She lived long enough to justify the original diagnosis of gall-bladder disease because when she came back on the eighth admission she had gallstones.

When the patient came in on the eighth admission she was a sick woman with frequent attacks of sharp pain, nausea, vomiting, gaseous eructations and questionable icterus, and she was in poor shape. The only extraordinary thing in this admission is the amylase of 116 units, which, if true, is certainly extreme. It makes one wonder if she had pancreatitis. Pancreatitis is certainly an overwhelming disease. She had an attack of pain but was not in any acute discomfort, and I am inclined to think that the amylase determination was an error. She was treated with penicillin, streptomycin and blood transfusions — again, a method of therapy consistent with the assumption that she had pancreatitis or something of that sort. Nothing was done until the twelfth day, when gallstones were removed and the common duct drained. A cholangiogram was done before discharge, which means that she had a T-tube in place and the idea was to carry out a protracted drainage of the biliary tree. That is what I get out of it. At readmission nothing is said about a biliary sinus or a biliary catheter. However, she was followed in the Out-Patient Department and did very well until just before the final admission, when she had an overwhelming onset of the final illness — an episode of anorexia, abdominal discomfort, nausea, vomiting and bleeding by rectum — and lapsed within two days into a state of

coma. On examination she was breathing heavily and was jaundiced. Obviously she had severe derangement of the bleeding tendency when she came back because the blood taken for prothrombin time did not clot, even after two hours. The blood hemoglobin was 15 gm., perhaps owing to hemoconcentration. The white-cell count was normal, the urine showed bile, and the stool was guaiac negative — a contradiction to the history of hematemesis and melena.

As I studied this case the question was obviously whether or not this was a complication of the former carcinoma in the form of hepatic metastases. It seems extremely unlikely that two months after cholecystectomy, at which time presumably the liver was not manifesting hepatic metastases, metastatic disease involving the liver from either of the previous carcinomas would occur. Of course the interesting thing is how rarely we see jaundice in cases of metastases involving the liver. Then the question is whether she was suffering from a complication of the cholecystectomy. We have been known to injure the common duct, even in this hospital, so that she could very well have had such a complication. Against that is the fact that following cholecystectomy she did well for two months. The terminal illness was abrupt — two days — and of severe onset. Were one large and several small stones removed and one that descended to cause another acute episode of obstructive mechanical jaundice left? I think that is rather unlikely. The lapse of the patient into coma, with a protracted prothrombin time such as that described here, sounds to me as if she had a profound visceral derangement of the liver, and that the terminal episode was one of liver failure — due to what, I cannot tell you. It is consistent with severe hepatitis or acute yellow atrophy or something of that sort.

What else could she have had? A hemorrhagic pancreatitis? At the final episode she complained of anorexia and of abdominal discomfort but nothing suggestive of the overwhelming onset of abdominal distress of pancreatic apoplexy. That is as far as I can go.

Dr. George Levene: Is the pain radiating back into the shoulder suggestive of pancreatitis?

Dr. Taylor: On the eighth admission she probably had something for which she was kept in the hospital for twelve days and given penicillin, streptomycin and transfusions. We have very few data given here, but everything was normal except for the elevated amylase. It must have been thought that she had a pancreatitis secondary to biliary-tract disease because biliary drainage was instituted, a T-tube put in place and a cholangiogram taken before she went home. Nothing is said about the state of the pancreas or the abdominal findings.

Dr. Louis P. Hastings: Dr. Taylor, did she have plasma transfusions a few months previously? What is the possibility of homologous serum hepatitis here?

Dr. Taylor: I think it is possible. We know that some of these patients have tremendously severe jaundice supervening on that basis. We certainly do not expect it with transfusion of whole blood as commonly as we do with plasma.

Clinical Diagnosis

Homologous serum hepatitis.

Dr. Taylor's Diagnosis

Hepatitis, with liver failure.

Anatomical Diagnosis

Homologous serum hepatitis.

Pathological Discussion

Dr. Benjamin Castleman: At autopsy this patient had a very small liver, weighing 700 gm.; it was soft, flabby, and brownish red, more so on the right side, with small, yellowish to grayish-white areas here and there. These grayish-white areas represented portal areas, and the reddish-brown areas represented the central parts of the lobule. In the central parts of the lobule the liver cells were wiped out completely and replaced by blood. This case represents an acute hepatitis of a fulminant variety and quite consistent with homologous serum jaundice. The patient had received three transfusions, and I have asked Dr. Soutter, who is in charge of the Blood Bank, to comment on the possible causes of the hepatitis.

Dr. Lamar Soutter: This case was of great interest to us because of our desire to avoid this complication. The possible source of homologous serum jaundice could have been from a needle or from a transfusion. For the past half year, at least, all hypodermic and intravenous needles in the hospital have been autoclaved so that the possibility of receiving hepatitis from another patient through the means of the needle is almost nonexistent. In

this case the other possible source is the transfusions. Out of 50,000 whole-blood transfusions from our Blood Bank this is the first case of homologous jaundice. Undoubtedly, there may be others in which the diagnosis was not made or the patient had a light case of jaundice not attributed to this source. It is possible for a person to have hepatitis or jaundice and not know about it — or not remember about it. We do not have any idea how long one is capable of carrying the virus before transmitting it to someone else. We do know that the incidence of homologous serum jaundice following whole-blood transfusion is infrequent as compared with that after dry plasma.

We investigated the donors of the three transfusions in this case. The first donor was a Negro boy, a professional donor of this hospital. He had been used before, and I am sure, after questioning him carefully, that he had no knowledge of ever having had any disease similar to jaundice or hepatitis. The second donor was a Red Cross volunteer, whose blood was sent to us by the Red Cross. I talked to him and found that there was no history of hepatitis or jaundice. The third blood came from an institution that establishes a credit in this hospital from which it can draw blood when needed. Unfortunately, although we believed that that institution had standards comparable to our own and observed the state and federal regulations regarding histories and physical examinations for donors, we found that it had collected blood at a prison but had neglected these matters. We assume that the blood that infected this patient came from that source, but of course there is no proof. The moral is obvious — a careful screening of donors must take place to keep down the incidence of the disease. I do not mean screening by the mere process of a technician asking the donor if he has had jaundice. But if a doctor will ask the donor if he has had "yellow jaundice" of the skin or scleras and will go into the symptoms of hepatitis, we may cut down on this unfortunate complication.

Dr. Richard B. Cattell: Dr. Castleman, have you ever observed this same picture in the liver in deaths following extensive disease with long common-duct obstruction due to stone?

Dr. Castleman: No, we never see it with stones. The liver, if involved, would be large, not small.

Dr. Cattell: I mean following operation for common-duct stones.

Dr. Castleman: Not so rapidly as this. The patient died within three days of the onset of symptoms. It was a fulminating form of liver disease. I do not believe I have seen obstruction that fast. Have you?

Dr. Cattell: No.

Dr. John Fallon: What did you find in the pancreas?

Dr. Castleman: Nothing. The common duct was not dilated, and there were no residual stones.

Dr. Taylor: The tube had been taken out after the final cholecystogram?

Dr. Castleman: Yes. A note was made to that effect in the Out-Patient Department record.

Dr. Taylor: I did not make out why, on the eighth admission, the patient was kept for twelve days on penicillin, streptomycin and transfusions — in preparation for a gall-bladder operation.

Dr. Castleman: It was thought that she had acute cholecystitis. She was very sick before operation.

Dr. Soutter: The cardiologists spent five days getting her ready for operation.

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IN UNION STRENGTH

THE proposal of the Blue Cross and Blue Shield plans to form a joint national association for more effective interstate operation has met with vigorous though not unexpected opposition. The proposed organization, under the name of Blue Cross-Blue Shield Association, Inc., was to have been a nonprofit membership corporation for the purpose of providing mechanisms for facilitating plan enrollment activities, collecting and interpreting experience data for all plans, basic underwriting and actuarial service for all plans, and the organization of Blue Cross-Blue Shield Health Service, Inc., as a stock insurance company. The object of the Health Service was to furnish coverage to employees of national firms where approved plans do not exist, and excess coverage where necessary; a central agency through which enrollment, billing and collection could be handled for nationally enrolled groups; uniform rates and benefits for all employees of nationally enrolled groups regardless of place of residence; and uniform regulations regarding enrollment, membership and administration of benefits. These provisions were to provide its sole purpose for existence.

Opposition to it was based on the fear that in union there is too much strength, that centralization of organization entails centralization of authority, that this country's cherished heritage of free enterprise would be placed in jeopardy, and that an organization for the control of medical practice would be ready at hand for the Government to take over at will.

Here there was present the usual basis of controversy — not between clear right and clear wrong — but between two arguments, each of which contains or seems to contain points in its favor.

Despite the dangers that were so clearly set forth by the opponents of the proposed association, it had to be borne in mind by the medical profession that the probable alternative to the acceptance of some larger and well organized voluntary prepayment plan for medical service would be a determined attempt at Government control as outlined in Mr. Ewing's recently publicized ten-year program. It seemed also apparent to many observers of modern political trends that the motto *E pluribus unum*, adopted at one time with a reasonable show of enthusiasm, may still have its virtue. The remark attributed to Benjamin Franklin after the signing of the Declaration of Independence that the signers would do well to hang together unless they wanted to hang separately indicates only that the advantages of united effort may sometimes outweigh its disadvantages.

The Blue Cross and Blue Shield Commissions were directed by the Los Angeles Conference of Blue Cross and Blue Shield plans in April, 1948, to revise the original proposals for a national association and submit them to the conference of plans to be held in October at French Lick Springs. This was done; the Blue Shield plans voted to submit the whole matter to the House of Delegates at its

meeting this month at St. Louis, and the Blue Cross voted to adopt the proposals but to defer action until after the same meeting.

The House of Delegates, giving as a main reason for its decision the possibility of Department of Justice action against a national company, voted to disapprove the association, favoring instead a national enrollment agency to co-operate in co-ordinating all prepaid health insurance plans. Such an agency would not be limited to sponsoring Blue Cross and Blue Shield plans alone.

The clear duty of the physicians of the country is now to support the actions and the decisions of their representative body, disregarding any differences of opinion that may previously have existed. The problems that lie ahead can be satisfactorily solved only by complete co-operation, and by recognition of the authority with which the House of Delegates of necessity speaks.

"FORSAKE NOT THYSELF"

THREE moral obligations implicit in the ministry of the physician are the subject of Dean Willard L. Sperry's talk before the staff of the Massachusetts General Hospital, published elsewhere in this issue of the *Journal*; they concern the practice of medicine, but they present also logical points of contact with the profession of ministering to the mind and to the soul. They are: to tell the truth, but so kindly that silence may sometimes take the place of words; to maintain at all times a sense of the sacredness of life; and to consider the individual at the expense of that abstraction known as mass man.

Judgment, as Hippocrates said, is difficult, and often the definition of a problem may be more stubborn than its answer. Moral judgments in particular may be relative, and the right of yesterday may be the wrong of today. Ethics can quickly change for the worse as well as for the better, and the change can be easily accepted, as was shockingly demonstrated during the years of Hitler's leadership in Germany. The principle of conscience, however, according to Dean Sperry's thesis "has an absolute warrant" and cannot change.

Often the moral choice that confronts the physician is not between black and white, where the just course is plainly marked, but between two shades of gray. Having chosen what seems to be the lighter shade he must go ahead "on the assumption that it becomes . . . a clear white." Tragedy is not a matter of a conflict between good and evil, but "a matter of a collision of two loyalties, each of which is wholly good on its own ground." This conflict has been tersely phrased by Richard Lovelace, whom Dean Sperry quotes:

> "I could not love thee, dear, so much,
> Loved I not honour more."

The ethics of truth-telling must be tempered with discrimination. Falsehood is not to be condoned, but as a matter of mercy and of what might be called the greater honesty, the absolute truth, or what it seems to be, may sometimes need to be withheld. Time, too, may suddenly so change the apparent facts that what was held to be the truth becomes an error.

The problem of euthanasia does not immediately or openly concern the physician, but it involves a principle on which he must take his stand. This must be settled for the physician as for the minister on the basis of a profound reverence for life. A deviation on the part of medicine from its basic principle of saving life must constitute a crack in its armor. "If we forfeit that reverence we have slipped our moral moorings . . . it is not our business to take life, only to try to save it."

In the face of mass evaluations of strong nationalistic and group trends, of the principle of the greatest good to the greatest number, the physician in partnership with the minister must continue to have faith in the value of the individual.

THE MEDICOLEGAL DEATH

FEW physicians, in all probability, are entirely clear in their minds as to the exact nature of their obligations to the state in the matter of death reports. Their medicolegal obligations, at least so far as these relations in the Commonwealth of Massachusetts are concerned, are admirably presented in the article by Ford published elsewhere in this issue of the *Journal*.

Certain categories of death, as set forth, must come under the jurisdiction of the medical examiner. These and certain others — hospital deaths within twenty-four hours of admission, hospital deaths when the decedent was unconscious on admission and remained so, any death pronounced by a physician other than the attending physician and any death when the patient was not attended by a physician within two weeks — must be reported to the medical examiner for his decision as to jurisdiction.

Deaths so reported in which the medical examiner declines authority may be certified by the attending physician if he is available and attended the decedent at least twice, one of which visits was within two weeks of death. Otherwise the board-of-health physician may make the certification.

The interest of the public is in discovering and solving crime and in protecting the public health where it may be endangered by virulent communicable disease, by industrial hazards or otherwise.

The friction that sometimes exists in metropolitan areas between the resident staffs of hospitals and the medical examiner's office over the performance of autopsies could be largely eliminated by a proper understanding by the former of the duties of the latter. These difficulties could largely be eliminated, as Dr. Ford says, "if each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital." If this were done, more cases would be available for hospital autopsy.

THE WASHINGTONIAN HOSPITAL

IN SPITE of many difficulties, the Washingtonian Hospital is carrying on. As the oldest hospital of its kind in the United States, it is continuing to make its contribution to the treatment of alcoholism. Because of its obscure location and quiet work, few people realize that behind its ancient façade patients with acute and chronic alcoholism are continuously being treated by psychotherapy and reflex conditioning. Alumni of the hospital have formed a "conditioning club" that meets semimonthly for group therapy with the medical director.

Last year 941 inpatients and 106 outpatients were given treatment. The average daily census is about 25. The bed capacity is 35.

Since its reorganization some ten years ago, it has continued its relation with the Community Fund. It maintains friendly relations with the Alcoholics Anonymous groups, but its main support comes from patients referred for treatment by private practitioners.

The Washingtonian Hospital, an institutional member of the American Hospital Association, is unique in offering the following services: treatment of acute alcoholic psychoses, acute intoxication without psychoses, cirrhosis of the liver, alcoholic neuritis, vitamin deficiency and malnutrition. It also institutes withdrawal procedures for certain alcohol and drug addicts. Other functions emphasized are efforts to rehabilitate alcohol addicts by psychotherapy, including some patients who require part-time hospitalization with working arrangements and social case work. Public education through addresses given to professional and lay groups is also emphasized. Consultative advice to social agencies and community leaders interested in problem drinkers is given.

In spite of the rising costs of medical care, the hospital is carrying on, mainly because a real need for it exists and because physicians practicing in Massachusetts know of its long service record and the accomplishments it has demonstrated in this uphill work.

MEDICOLEGAL ABSTRACT

Liability for Malpractice — Administration of narcotics. A recent Massachusetts case involved questions of such general interest in connection with the liability of physicians for their administration of narcotics that a brief was filed in the case in behalf of the Massachusetts Medical Society.

The testimony in the case was wholly contradictory on the essential questions of how much morphine was given and under what circumstances it was given. The evidence in its aspect most favorable to the patient, who sued the doctor, was that on December 25, 1939, she was suffering from

nausea but without pain; that the defendant, without any complaint of pain by her and without any physical examination or questions regarding medical history, gave her a hypodermic injection of morphine, which was repeated twice that day; that early in 1940 the defendant gave her another injection in similar circumstances; that in 1941 the defendant gave her occasional injections until by July she was receiving about two injections a week; that by the end of August he was giving her an injection every day, in September twice a day, and in October three times or more a day until the patient's husband ordered the defendant from the house and threatened to "clean him up"; that thereafter the patient became "jumpy and nervous"; and that two days later, after telephoning about every doctor in the town for morphine, the patient experienced a complete black-out and was taken to a hospital suffering from morphine addiction and described as "one-quarter of the way along to confirmed addiction." The patient testified in effect that she had never stated that she had pain until after the defendant had ceased giving her the injections. There was medical testimony that it was not proper medical practice to administer morphine to a patient who complained of nausea but not of pain, or over a period in which there was no pain involved, or to continue giving morphine in the absence of a diagnosis of a condition that could not be cured.

There was evidence that another physician had given the patient codeine from 1939 on and during the period in which the defendant was treating her. There was also evidence that the patient had taken quantities of phenobarbital at some time, although it was not shown that she had taken phenobarbital during the period when she was receiving frequent injections of morphine from the defendant. Therefore, the question was presented whether the patient's condition when she was taken to the hospital was caused by morphine administered by the defendant or by other drugs. The court held that there was ample evidence, presumably the diagnosis of her condition as morphine addiction, to indicate that her condition was proximately caused by morphine administered by the defendant.

The court does not explain in what sense the injections given by the defendant caused the patient's condition. The court presumably meant that the jury could have believed that the injections given by the defendant were sufficient by themselves to account for the patient's condition or that the defendant's treatments would have caused some kind of breakdown by themselves although the patient's condition may have been aggravated by the codeine and phenobarbital. There is a sense in which a doctor may be said to have caused an addiction if his patient merely learns to like the effect of a drug from his injections, and the patient, afterward satisfying her taste from other sources, becomes an addict. The court apparently did not regard the case before it as such a case, and it did not decide what rule should be applied in such a case.

The defendant argued that the plaintiff sought the morphine she got from him, knowing the risks involved and voluntarily assuming them. The court did not deny that she would be barred from recovery if such testimony were true but rejected this argument for the reason that on the evidence the jury could have found that she did not know or assume the risks. The plaintiff herself testified that if not at first, at least eventually, she sought the injections she received from the defendant. She testified that by about the last of July, 1944, she was "beginning to get a little sneaky — starting to lie" and did not always tell the defendant the truth about her condition. She testified that she did not know what the defendant was giving her, although in July she had a "suspicion," and she knew that it was something that was relieving her and making her feel "pretty high." The court concluded:

> From this, together with other evidence that need not be stated, the jury could have found that she knew she was getting morphine, but they were not obliged so to find. Much less were they obliged to find that she knew at what point addiction would begin, or that at any time before addiction became a fact she had ceased to rely upon the superior knowledge of the defendant as to the amount of the drug that could safely be taken over a given period of time. There was medical evidence that a person could become addicted "without knowing it."

The court plainly implied that after addiction has become a fact the patient might not be wholly responsible for her actions in attempting to get morphine injections and might not be barred from recovery on the ground that she assumed the risks. It is obvious in this case that when the patient started lying to the defendant to obtain morphine injections she had ceased to rely on the superior knowledge of the defendant and begun to assume the risks herself. The court must have thought that the jury could find that this was after the addiction was a fact. The time of addiction, therefore, becomes an important issue in cases such as this.

It was argued in the case that the patient by "lying" to obtain morphine injections was guilty of a criminal offense, which should prevent her from holding the doctor liable. However, the court held that the statute, which applied only to lying "for the purpose of procuring a prescription for, or the delivery of, a narcotic drug," was not applicable to a case of misrepresentation for the purpose of obtaining an injection personally administered by the doctor, such an injection not being a "delivery" within the meaning of the statute.

The court held that on this evidence, the jury could render a verdict for the plaintiff, even if they need not have done so. Reassuring the medical profession the court said:

> This decision rests upon evidence of improper and unprofessional conduct on the part of the defendant leading to addiction in the plaintiff. . . . Nothing contained herein need cause anxiety to an honest physician who administers narcotics to a patient in accordance with the prevailing standards of medical practice.

This reassurance must be read in the light of the practical difficulties of proof that may be involved. In any case an honest doctor takes the risk that his testimony may not be believed. For example, in the case before the court, if the defendant's records and testimony had been believed, he would have appeared to be an honest physician administering narcotics to a patient in accordance with the prevailing standards of medical practice. The jury, however, apparently believed the patient's testimony, and this required the court to view the defendant's conduct in a different light. (*King* v. *Solomon*, 1948 Mass. Adv. Sh. 1005.)

CORRESPONDENCE

UNIVERSITY OF ROCHESTER TRAINING PROGRAM IN PSYCHOTHERAPY

To the Editor: I have read with great interest the article entitled "Medical Schools and the Quality of Medical Care," by Dr. E. Richard Weinerman, which appeared in the November 25 issue of the *Journal*. I think that you are doing the profession a great service by publishing articles (and editorials!) on the subject of modern medical training and its socio-economic aspects. This is a timely reminder for those of us who, as students, find ourselves confronted with a maze of material in clinical medicine and who may therefore lose sight of the other implications of disease.

Nevertheless, for the sake of the record, I should like to point out that at the University of Rochester, under the expert guidance of Dr. John Romano, a well integrated program of training in psychotherapy has been initiated. This program began two years ago and now applies to students in all years. A new building has recently been erected for the hospitalization of patients with mental illness, and students in their third and fourth years are receiving intensive training in this new clinic. The course given here not only includes the study of basic psychiatry but also considers the ancillary disciplines of sociology and economics, as presented in lectures by persons who head the social service at the Strong Memorial Hospital.

Most of the students realize the great importance of this aspect of medical training — and not only of medical training, but of medical living and thinking, if I may call it that.

Articles like Dr. Weinerman's are therefore highly welcome and I hope that others on this vital topic will be forthcoming in your splendid *Journal*.

Ernest L. Levinger
Third-Year Student
University of Rochester School of Medicine

BOOK REVIEWS

Unipolar Lead Electrocardiography*: *Including standard leads, unipolar extremity leads and multiple unipolar precordial leads. By Emanuel Goldberger, B.S., M.D. 8°, cloth, 182 pp., with 88 illustrations. Philadelphia: Lea and Febiger, 1947. $4.00.

Dr. Goldberger's book is really the first devoted almost exclusively to the subject of unipolar leads. Although these leads were studied and described by Wilson many years ago, they have come into general use only recently. The literature on this subject is growing rapidly but there has been a real need for a textbook to explain the theory and define the uses and limitations of unipolar leads. Dr. Goldberger's book fills this requirement in part.

The presentation of material is an orderly one, beginning with an explanation of underlying theory, continuing with detailed instructions for taking leads and ending with a discussion of their clinical application.

Reasonable objections can be raised to the rather dogmatic way in which the subject matter is presented. Nevertheless, the book serves a very useful function in placing proper emphasis upon the origin of extremity lead patterns from basic patterns in the heart itself. Dr. Goldberger's approach also serves to emphasize heart position in relation to the recording electrodes. This represents another step away from purely empirical interpretation even though one does not agree with every statement the author makes. This monograph is not intended as a complete textbook, and therefore detailed evaluations of unipolar leads cannot be expected. This book is recommended to all who are interested in electrocardiography.

The Epithelia of Woman's Reproductive Organs*: *A correlative study of cyclic changes. By George N. Papanicolaou, M.D., Ph.D., Herbert F. Traut, M.D., and Andrew A. Marchetti, M.D. 4°, cloth, 53 pp., with 22 plates. New York: The Commonwealth Fund, 1948. $10.00.

This monograph records a decade of painstaking correlative research at Cornell University Medical College, sponsored by the Commonwealth Fund and conducted by three professorial experts in the fields of microscopical anatomy, biology, physiology and gynecology. The epithelial cytology of the normal human female reproductive tract is extensively examined, and its changes intensively studied in relation to the menstrual cycle. The results are embodied not only in the text but also in a large, colored folding chart, and are amplified and presented in twenty-three full-page plates of drawings and colored photomicrographs. There is a foreword by Dr. Joseph C. Hinsey, dean and professor of anatomy at Cornell University Medical College. In their introduction the authors review the literature of the subject, especially the epochal work of Rock and Hertig in the classification of the menstrual cycle, which is recorded in a bibliography of ninety titles.

This volume represents a monumental piece of research of permanent value, for it goes far to clarify and complete knowledge in the field and subject with which it deals, and was made possible by the intelligently co-ordinated and directed skills of investigators, technicians, and clinicians working harmoniously in a common enterprise toward a common objective.

NOTICES

POSITIONS FOR CIVILIAN DOCTORS IN PANAMA

Permanent appointments, in the Civil Service, for physicians now exist in the Panama Canal Medical Service. Salaries range from $5599 to $7794, with free transportation to the Canal Zone provided for physicians, their families and household goods. Return transportation is furnished upon completion of a minimum of one year's service. In addition, doctors who receive appointments get two months' paid vacation (including time lost by illness) and reduced fares on Panama Canal passenger vessels.

Requirements for position paying $5599 to $6540 are: graduation from an approved medical school; license to practice medicine in a state; ability to pass a standard physical examination; and completion of one year of internship in a hospital approved by the American Medical Association.

Requirements for positions paying $6540 to $7794 are the same except that a minimum of three years of post-internship experience is required.

Physicians who are interested in a position as medical officer in the Panama Canal Zone should communicate with Chief of Office, The Panama Canal, Washington, D. C. Applications may also be submitted to the United States Civil Service Commission, Washington, D. C.

(*Notices concluded on page xi*)